ARCHIVES OF
DISEASE IN CHILDHOOD

INCORPORATING THE BRITISH JOURNAL OF CHILDREN'S DISEASES

EDITORS

P. R. EVANS and I. A. B. CATHIE

CONTENTS

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

NOTICE TO CONTRIBUTORS

Papers for publication should be sent to Dr. I. A. B. Cathie, The Hospital for Sick Children, Great Ormond Street, London, W.C.1.

Submission of a paper for publication will be held to imply that it contains original work which has not been previously published. Permission to republish must be obtained from the Editors.

Papers should be as concise as possible and illustrations kept to the minimum. Manuscripts should be typewritten top copies in double spacing. They should have been carefully revised, and alterations in proof, apart from printers' errors, are not permissible.

Photographs and photomicrographs should be submitted unmounted. Drawings and diagrams should be boldly drawn in black ink on stout white paper. Any necessary lettering may be lightly inserted in pencil.

Overseas contributors should nominate somebody resident in Great Britain willing to correct their proofs and deal with the subject of reprints.

Current numbers of the *Archives of Disease in Childhood* should be consulted for information concerning standard abbreviations, etc. In references to papers in the text the year of publication in parenthesis should follow the author's name. References at the end of the text should be in alphabetical order of authors' names, and titles of journals should be abbreviated according to the *World List of Scientific Periodicals*. Book titles should be followed by the place of publication.

Failure to observe the above directions may result in the return of typescripts to authors for correction, with consequent delay in publication.

Twenty-five reprints are supplied free. Further reprints must be ordered when returning proofs.

Subscription. £1 3s. 0d. per annum, post free.

Applications for advertising space should be made to the Advertisement Manager, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

SOME RADIOGRAPHIC MANIFESTATIONS OF EARLY SCURVY

BY

JAMES F. BRAILSFORD

From the Royal Orthopaedic Hospital, Birmingham

Though scurvy is associated with characteristic radiographic appearances it is important to realize that it can manifest itself clinically before radiography detects any change from the normal in the bones. The latent negative radiographic period may be of several months. In most conditions it varies with the individual and the factors which are associated with the deficiency. There is some evidence that the deficiency factors, as in rickets, act upon the foetus *in utero* and in the early days of separate life, though scurvy is commonly regarded as a deficiency disease which shows itself between the eighth and eighteenth months. The initial lesion which usually attracts clinical attention is the haematoma. Hutchinson and Moncrieff (1941) have pointed out that

'the chief changes in infantile scurvy are in the neighbourhood of the bones. A section made across a limb at the site of a swelling shows that the periosteum is hypervascular, thickened and separated from the subjacent bone by a layer of partially organized blood clot. There is no sign of inflammation and no hard bone is formed in the periosteum except in longstanding cases.'

Therefore, in these early cases we see no sign of change in the bones. The first radiographic evidence may be a subperiosteal haemorrhage (Fig. 2) or fractures at the growing extremity of one or more of the long bones (Fig. 1), but usually such lesions have been present for a week or more before radiographic examination has been made, for we often see that already some calcium has been deposited in an amorphous form within the associated haematoma, and is most evident at the periphery of the haematoma, leaving a translucent zone between it and the periphery of the shaft of the bone (Fig. 2).

Infants, apparently healthy in other respects, have been seen at birth with considerable calcium in haematomata associated with fracture, indicating intra-uterine damage of some weeks' duration. Massive haematomata with much calcium surrounding both femora of an unusual infant at birth have

been illustrated (Brailsford, 1948). Certainly, within the first few months of life radiographs may show amorphous calcium deposition in haematomata enveloping one or more long bones, which appear to have normal structure and density, and, though no other definite indication of scurvy may be present, organization, ossification and complete restitution to normal bone takes place readily on the administration of vitamin C. These features are illustrated by the sequence of radiographic changes in Fig. 2.

Fig. 2 illustrates the case of an infant, aged 3 months, who developed a swelling in the left thigh. A radiograph of the thigh on August 15, 1947 (Fig. 2A), showed amorphous calcium deposited in a large subperiosteal haematoma which enveloped most of the shaft of the femur. A further radiograph (Fig. 2B) on August 28, 1947, showed an increase in the size of the lesion, and its definition suggested that rapid organization and ossification was taking place. The radiograph of September 8, 1947 (Fig. 2C), shows that within a month most of the haematoma had been converted into bone. On the clinical and radiographic evidence this was interpreted as sarcoma and drastic treatment was contemplated. The films were submitted to me by Dr. Patricia Franklyn, and I suggested that the condition was due to scurvy and advised the administration of appropriate amounts of vitamin C. With its exhibition the patient rapidly showed signs of recovery and by January 8, 1948 (see Fig. 2D), considerable resolution had taken place. By 1952 the bone had returned to normal (Fig. 2E). Obviously in this case the clinical signs of scurvy were not present and the radiographic evidence had been misinterpreted but the therapeutic test was both positive and spectacular.

In 1943 in a paper on osteogenesis imperfecta, I published an account of four patients with this dystrophy who developed an unusual complication, namely, the development around one or more bones of a swelling, probably as the result of trauma, since it was observed that a similar sequence of changes
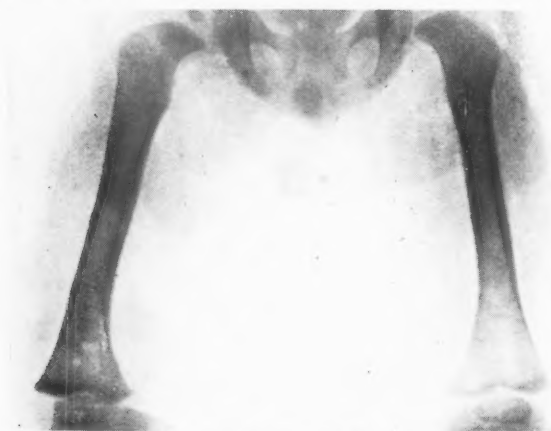
7
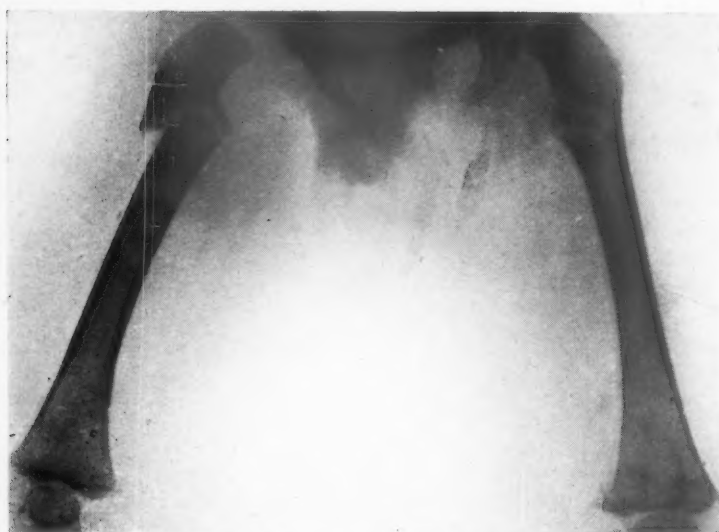
A.—On admission on January 19, 1948, fractures at the lower ends of the femoral diaphyses and a subtrochanteric fracture of the upper third femur are seen.

B—After anti-scorbutic feeding.

C—Almost complete resolution of haemorrhages.

took place at the site of surgical injury. The trauma was such that it escaped the attention it demanded. Radiographs of the recent swelling of the inner side of the right femur showed the rounded outline of a large, soft-tissue mass. Its almost sudden appearance, its extent and its clearly defined rounded border indicated that it was probably a haematoma. Other tumour masses in the same and adjacent limbs suggested masses of longer duration presenting the appearances which, after a sequence of changes, developed in the most recent (Fig. 3A). The serial radiographic appearances of these lesions were identical with those seen in haematomata, that is, large, rounded, soft-tissue swelling around the bone of an acute haematoma which gradually took on a cloudy and later a granulated appearance. The greater density indicated calcium deposits in the haematoma but in this condition the calcium deposit is denser than in haematomata associated with normal bone. With the passage of time organization of

the calcium and ossification was indicated by the diminishing mass and the corrugated appearance of its shrunken periphery, and gradually by the definition and density of the bone. The new bone persisted in its irregular form and the details of the enveloped femoral shaft were completely absorbed (Fig. 3B).

This is a very unusual sequence of changes for osteogenesis imperfecta, in which are usually seen fractures which heal without any undue callus formation or around which there may be little evidence of callus, the fragments remaining disunited for many years or even throughout a subsequent long life. There is only one other condition which resembles it, the haematoma which forms at the site of a fracture of a bone of a paralysed limb of an otherwise normal skeleton. I have no doubt about the haematoma being due to injury in such cases, and the resulting bone deformity does not undergo the ready moulding seen in the normal limb (Figs. 4A and B) but there was no indication of paralysis in these patients.

I was led to consider the factor which could be responsible for multiple haemorrhages on relatively slight trauma, and the possibility of the added complication of scurvy suggested itself. Scurvy is the only condition, apart from haemophilia and leukaemia and other conditions, with their characteristic clinical signs and symptoms, in which are seen multiple sites with subperiosteal haematoma around bones which may be apparently normal radiographically. But in scurvy the haematomata are readily organized on the administration of vitamin C. They follow a definite sequence of changes. They calcify and become ossified, the new bone is gradually absorbed, and finally the affected bone becomes and remains indistinguishable from the normal in

shape and size and structure (Figs. 1 and 2). In osteogenesis imperfecta we see the initial stages as far as ossification, but not the gradual restitution of the bone to the normal. We must however remember that osteogenesis imperfecta is what its name implies, an imperfect ossification, seen in the disturbed growth at the metaphyses (Fig. 3B), and it seems reasonable to suggest that this disturbance in growth is responsible for the bone of unusual character, organized from haematomata, seen in osteogenesis imperfecta. There had never been any suspicion in my mind of sarcoma; the radiographs illustrated a benign lesion which resolved.

Baker (1946) described two similar cases under the title 'Hyperplastic Callus Simulating Sarcoma in Two Cases of Fragilitis Ossea'. One of these children falling had sustained a fracture through the femoral shaft around which a large mass formed. Five weeks later it was extensively explored for a complete biopsy. This was considered to show chondrosarcoma, but amputation was regarded as too risky and of doubtful value. Although after operation the thigh swelled excessively so that the tumour appeared to fungate through the skin, it subsided and the bony lesion resolved in the manner I have indicated. As Baker commented, 'Had the limb been removed . . .

FIG. 2.—A—Radiographs of the limbs of an infant aged 3 months on August 15, 1947, with early scurvy. The right thigh shows a fusiform tumour with calcification in a large haematoma. The calcium is in an amorphous form, is ill-defined, and is separated from the cortex of the femur by a parallel translucent zone. The diaphysis and the epiphyses of the left femur and tibia are normal in appearance.

B—The right thigh on August 28, 1947, showing that some organization of the calcium has already taken place.

C—Same limb on September 8, 1947, after administration of vitamin C had been started. The mass has now been converted into bone with good definition.

D—Same limb on January 8, 1948, when considerable resolution has taken place.

E—Same limb on August 30, 1949. The bone has now almost normal→ characteristics. The epiphyses show no sign of past scurvy.

A

Fig. 3.—A—Radiograph on April 7, 1936, showing multiple haematomata at different ages. On the medial aspect of the femur on the right side is the most recent, on the lateral aspect an older lesion undergoing organization, and on the left side the haematoma has become ossified and is shrunken.

B—The same femora three years later showing absorption of the original cortex and irregular new involucrum. Note the characteristic irregularity of osteogenesis imperfecta on the borders of the metaphyses at the lower ends of the femora.

B

it would have been impossible to prove that it was not a sarcoma cured by amputation,' yet the radiographs show the sequence of changes I consider typical of haematoma. Fairbank and Baker (1948) and Watson-Jones (1952) support Baker in his revised description of the pathological condition as hyperplastic callus, although there is radiographic evidence of a similar evolution of haematomata in scurvy. Neither of these writers gives any explanation for the unusual development, nor supplies any evidence on which scurvy can be excluded, since the positive response to the therapeutic test is probably the most reliable, and probably the only supporting, evidence.

Ossifying haematomata, not only in scurvy and osteogenesis imperfecta, but also in limbs with neurovascular disturbances and in haemophilia, and even at the site of unsuspected fractures, have been mistaken from their clinical and histological evidence for sarcoma and amputation has resulted when the patients were considered to be fit enough to stand the operation. Undoubtedly some of these cases are regarded as 'cures by amputation'.

Accounts of many cases of infantile cortical hyperostoses have been published since the condition was first described but they have added little to the original description by Caffey and Silverman (1945). No adequate explanation has been put forth. It is stated by many that there is no evidence of scurvy, syphilis, or rickets and that the lesions invariably resolve without any specific treatment. It may be that the observers have looked for gross evidence and have not appreciated that scurvy may exist in certain cases before such gross evidence has been revealed. It has been indicated that it can occur without the

bones showing any evidence of departure from the normal texture and density, one or more fractures being the only radiographic evidence to indicate abnormality even though clinically the infant may show profound malnutrition. Fig. 1 shows the

appearance of the bones of such an infant aged 11 months. There is no radiographic indication of scurvy though the patient was markedly emaciated and had obviously been seriously neglected. The fractures had been present for 10 to 14 days before there was any radiographic evidence of the sub-periosteal haemorrhage but it was clear that other fractures had occurred and had resolved without their presence being suspected. The rapid improvement in the clinical condition following adequate food containing fresh fruit juices and codliver oil led to the development of a fine healthy infant of nearly twice the weight within a few months. The clinical improvement was associated with calcification and ossification of the haemorrhagic foci, and within six months even the more massive periosteal masses of irregular new bone had been absorbed.

That deficiency and endocrine imbalance can be demonstrated in infants at birth we know from studies of foetal rickets and hyperparathyroidism. We know also that one of the earliest signs of scurvy is subperiosteal haemorrhage which may be so large as to be detected clinically, yet the radiographs may show apparently normal bone for a week or more, and only when sufficient calcium has been deposited to give contrast above that of the soft tissues can we see the size and position of haematomata. Certainly not until then can we detect clinically or from the radiographs subperiosteal haemorrhage of a minor degree such as could lead to the production of the radiographic appearances of cortical hyperostoses. The statement that the hyperostoses resolve with no specific medication tends to underestimate the attention which would be given to the feeding of the infants in whom these lesions have been found. This response could be regarded as the positive thera-

FIG. 4.—Radiographs of a paralysed limb.

A—Radiograph on September 15, 1947, showing calcification and ossification around fractures of the upper thirds of the tibia and fibula one month old.

B—Radiograph on June 1, 1949, showing the unusual ossification of the upper third of the tibia at the site of the haematoma, also more recent fractures of the lower thirds of the tibia and fibula with subperiosteal haemorrhages.

peutic test of scurvy. Such children would certainly be given adequate vitamins in their food; it would be unreasonable to deprive them to prove that lack of vitamins checked resolution. As will be seen from Fig. 2 the radiographic appearances of the bones are normal; there is no indication in their shape, texture, density or growth centres of scurvy; only the signs of resolution in a large haematoma indicated this. Clinically that lesion was interpreted as a sarcoma, and the radiographic evidence was thought to support this and amputation considered, but following the author's interpretation of scurvy the lesion completely resolved on the administration of vitamin C.

What is difficult to understand is the relatively sudden outburst of so many cases. Many, it would seem, develop in the U.S.A. Some isolated cases have been reported elsewhere. In Birmingham I did the radiography for all the infant welfare clinics of the city for over 20 years and never met with one such case. The suggestion could be made that such cases were not sent for radiography, but, with the prominence of the local signs, such suspicion of neglect of investigation on the part of the clinicians concerned I should regard as unreasonable, bearing in mind the triviality of the clinical signs in patients who were sent for radiography.

Multiple biopsies have been performed on many cases of infantile cortical hyperostoses but no evidence of any value for the understanding of the condition has been so obtained. Indeed biopsies could only disturb and delay complete resolution of lesions which, untouched, have been shown to resolve completely within the minimum of time. Explorations are not made before the lesions have shown considerable resolution; the evidence presented then indicates that even the nature of the lesion could not be determined.

It may be that some deleterious factor for the foetus and infant is operating through the mother. I have evidence which indicates that the mother can transmit a 'resistance' to ordinary doses of vitamin D and calcium; further, not all the physical and chemical factors exhibited, with or without the knowledge of the doctor, during the care of the mother are necessarily beneficial to the welfare of the infant. And in any discussion of the conditions which are associated with the radiographic appearances of periosteal irregularities the effects of the administration of vitamins must be considered. I saw one infant with the typical radiographic evidence of scurvy, to whom, under medical supervision, massive doses of vitamin D had been given over a long period. The skeleton gradually became denser and denser until it became of the density of Albers-Schönberg's disease. The haematomata did not show the healing response seen after vitamin C but persisted and developed an even greater density before the infant died.

The radiographs of infants between the ages of 6 months and 3 years, who have had excessive vitamin A, show some periosteal reaction and increased density at the growth extremities of the diaphyses, but, unlike cases showing infantile cortical hyperostoses, the metatarsals show periosteal accretions. Arena, Sarazen and Baylin (1951) reported hypervitaminosis A in one infant of 6½ months. Radiographs showed craniotabes and periosteal accretions which readily resolved when administration of vitamin A ceased. Chronic poisoning due to excess vitamin A has been discussed and recorded by Caffey and Silverman (1945). Two of their cases showed periosteal accretions resembling the less severe cortical hyperostoses at the late age of 25 months, but no facial swelling or hyperostoses of the mandible. Seven of the patients had been given excessive amounts of vitamins A and D over long periods. The limbs were swollen and painful. The ribs, clavicles and long bones showed periosteal changes, but those bones which were unaffected seemed to be normal in appearance. Improvement was noted within a few days of stopping the intake of vitamins and the hyperostoses gradually resolved. (The vitamins are usually administered in oleum percomorphum which is said to contain 60,000 units of vitamin A and 8,500 units of vitamin D per g.) Such preparations are readily available in the drug stores without any need for medical supervision.

During my tour of the U.S.A. during 1948 and 1949 in the popular magazines and in the parlour cars of the trains I could not but overhear from members of the public of their common use, Indeed throughout that tour I 'learnt' more in this way of allergies, infections, isotopes and the need for shots, vitamins and periodic changes in babies' formulae than in any period of my medical career.

Summary

The well recognized clinical and radiographic signs of scurvy are usually not seen until the infant is 8 to 18 months of age, but the earliest radiographic signs may be those of fracture with a surrounding haematoma. In some cases such lesions may be seen without any definite clinical evidence of scurvy; in other cases emaciation and other signs of neglect may be present and yet the bones may have normal radiographic density and regularity.

The recent haematoma can be suspected from the presence of a fusiform soft-tissue swelling; the radiograph will reveal no more at this stage, but within seven to 14 days radiographic signs of the deposition of amorphous calcium can be detected towards the periphery of the haematoma. This is followed by a denser granular deposition and later its organization into bone when it shrinks and loses its regular peripheral outline. The lesion may be mistaken clinically, histologically and radiographically for sarcoma, but with vitamin C medication the ossified haematoma is gradually absorbed and the bone is left with normal features as distinct from the scurvy of the later age period. The radiographic features of unusual haematoma seen in certain cases of osteogenesis imperfecta and paralysed limbs and the lesions of infantile cortical hyperostoses are considered in relation to the sequence of radiographic changes in the lesions in scurvy. The best proof of scurvy may be the response to the therapeutic test—complete resolution of the lesion when adequate vitamin C is administered. The effect of vitamins on the bones is described.

REFERENCES

Arena, J. M., Sarazen, P. and Baylin, G. J. (1951). *Pediatrics*, **8**, 788.
Baker, S. L. (1946). *J. Path. Bact.*, **58**, 609.
Brailsford, J. F. (1943). *Brit. J. Radiol.*, **16**, 129.
—— (1948). *The Radiology of Bones and Joints*, 4th ed. London.
Caffey, J. and Silverman, W. A. (1945). *Amer. J. Roentgenol.*, **54**, 1.
Fairbank, H. A. T. and Baker, S. L. (1948). *Brit. J. Surg.*, **36**, 1.
Hutchison, R. and Moncrieff, A. (1941). *Price's Textbook of Medicine*, 6th ed., p. 454.
Watson-Jones, R. (1952). *Fractures and Joint Injuries*, 4th ed. Edinburgh.

FOUR CASES OF ACUTE ACQUIRED HAEMOLYTIC ANAEMIA IN CHILDHOOD TREATED WITH A.C.T.H.

BY

B. S. ROSE and S. N. NABARRO
From the General Infirmary, Leeds

In the early years of the present century the French school of haematologists appreciated that acute acquired haemolytic anaemia was dependent upon the presence of abnormal antibodies in the blood (Chauffard, Troisier and Vincent, 1908; Hayem, 1908; Widal, Abrami and Brulé, 1907).

During the first world war this important work was largely forgotten. Although Lederer (1925, 1930) gave his first classical description of the clinical picture in 1925, it was not until 1940 that Dameshek and Schwartz (1940) again stressed the immunological aspects of the disease. More recently, improved technical methods (Dacie and de Gruchy, 1951) have made possible the demonstration of abnormal antibodies in many cases in which gross agglutination is absent, thus confirming the early studies. The reason for the development of these abnormal antibodies is still obscure, but an infective origin for acute acquired haemolytic anaemia has long been postulated. This theory has recently received some support from the work of Hagberg (1952). He was able to demonstrate considerable diminution in the survival time of normal red cells transfused into children suffering from apparently simple post-infective anaemia.

The knowledge that A.C.T.H. and cortisone interfere with antibody reactions has given fresh significance to these findings. During the last two years numerous reports (Best, Limarzi and Poncher, 1951; Crary and Beck, 1952; Dameshek, 1950; Dameshek, Rosenthal and Schwartz, 1951; Dameshek and Rosenthal, 1951; Davidson, Duthie, Girdwood and Sinclair, 1951; Etess, Bassen, Litwins and Sussman, 1951; Gardner, 1950; Gardner, McElfresh, Harris and Diamond, 1951; Langeron, 1951; Ley and Gardner, 1951; Mallarmé, Martin, Eyquem and Fleury, 1951; Meyer, 1951; Rosenthal, Spaet, Goldenberg and Dameshek, 1952; Unger, 1951; Young, Christian and Izzo, 1951) have dealt with the use of these drugs in the treatment of acute acquired haemolytic anaemia. Formerly, Dameshek

and Schwartz (1940) drew attention to the value of splenectomy when blood transfusion alone was proving to be inadequate.

Four cases of acute acquired haemolytic anaemia were admitted to hospital during a period of 16 days in March, 1952. The weather at the time was cold and damp. All four children lived in Leeds; two (H.S. and J.G.) in adjacent streets of a modern estate four miles from the centre of the city; one (V.E.) in a poor district three miles distant from the hospital; and the fourth (V.P.) on the outskirts of the city, some six miles from the other children. None of the children attended the same school, nor had any contact with the others before this illness.

Because of the poor response to blood transfusions of three of these children (V.E., J.G. and H.S.) it was decided that A.C.T.H. should be tried.

Clinical Summaries

Case 1. V.E., a girl, aged 6 months, had no relevant family or personal history of previous illness. She was admitted with two days' history of pallor, cough and fretfulness. On examination, she was collapsed, pale and slightly icteric, with severe cough and dyspnoea. The pulse rate exceeded 140 per minute and the temperature was 101·2° F. There was no clinically detectable enlargement of liver, spleen or lymph nodes, and no haemorrhages were found. The retinae were normal. Numerous râles were present in all areas of the lungs. Subsequent x-ray examination showed multiple opacities, most marked at the left apex. Haemoglobinuria, absent on admission, developed at the time of a relapse which took place during the eighth to tenth weeks in hospital.

The blood count on admission showed haemoglobin 12% (Sahli), red cells 790,000 per c.mm., colour index 0·89, leucocytes 17,200 per c.mm. (polymorphs 53%, metamyelocytes 5%, myelocytes 1·5%, lymphocytes 38%, basophils 2·5%) and nucleated red cells 8 per 100 white cells.

The red cells showed moderate anisocytosis and marked polychromasia. There was a moderate neutrophilia with a shift to the left in the Arneth count. No

primitive cells were seen and the platelets were normal. The bone marrow showed intense normoblastic hyperplasia, with no evidence of leukaemia. The serum bilirubin level was 2·2 mg. per 100 ml., and there was an excess of urobilinogen in the urine. Warm and cold auto-agglutinins and warm iso-agglutinins were present during the active phase, making cross-matching difficult on several occasions. A severe relapse occurred after each of five transfusions. The baby was therefore given A.C.T.H., to which she responded well. On withdrawal of the drug she rapidly relapsed, and it was decided that splenectomy should be performed during a second course of A.C.T.H., as three further transfusions had been necessary. The splenectomy had no apparent effect, and she relapsed again when A.C.T.H. was withdrawn for the second time. A third course of A.C.T.H., later changed to cortisone, has therefore been given, and on this occasion, on withdrawal, 28 weeks after the onset of the illness, there has been no relapse. The direct Coombs test has remained positive from the outset, but is now only weakly positive. The early progress and treatment are shown in Fig. 1, and the results of virus studies in the Table.
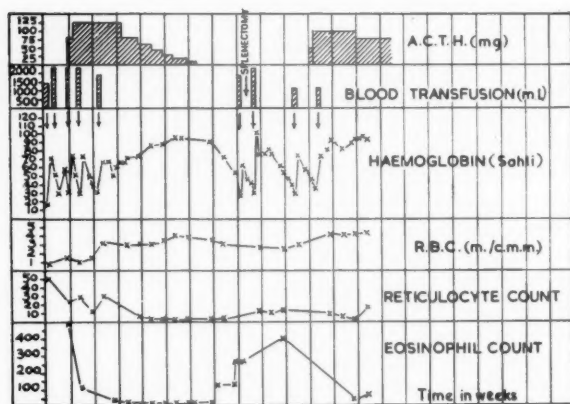

FIG. 1.

Case 2. H.S., a girl, aged 3 years, had no relevant family or personal history of previous illness. She was admitted with one week's history of listlessness, which in the last two days had become extreme, culminating in coma. She had been vomiting for 24 hours, and had passed red urine on the day before admission. On examination, she was comatose and extremely pale, with air hunger and gross retinal haemorrhages but no other evidence of bleeding. She was afebrile. There was no clinically detectable enlargement of the liver, spleen or lymph nodes. There were no significant signs in the chest, and subsequent x-ray examination proved to be normal. Gross haemoglobinuria was present during the first two weeks in hospital.

The blood count on admission showed: Haemoglobin 21% (Sahli), red cells 1·3 m. per c.mm., colour index 1·3, leucocytes 31,800 per c.mm. (polymorphs 64%, metamyelocytes 8%, myelocytes 1%, lymphocytes 36%) and nucleated red cells 20 per 100 white cells.

The blood film showed a reactive leuco-erythroblastic picture, with no evidence of leukaemia. The platelets were normal. Marrow biopsy was not performed. The serum bilirubin level was 2·6 mg. per 100 ml., and the faecal urobilinogen 268 mg. per 100 g. There was an excess of urobilinogen in the urine. The results of the initial Coombs test are unfortunately not available, but tests in the fourth and twelfth weeks were negative. Warm auto- and iso-agglutinins were present during the first week, and warm and cold iso-agglutinins were still readily detectable in the sixth week. As the child relapsed rapidly after each of three transfusions and remained desperately ill, A.C.T.H. was given over a period of five weeks. She responded well, and there has been no subsequent relapse. The Coombs test remained negative. The early progress and treatment are shown in Fig. 2.
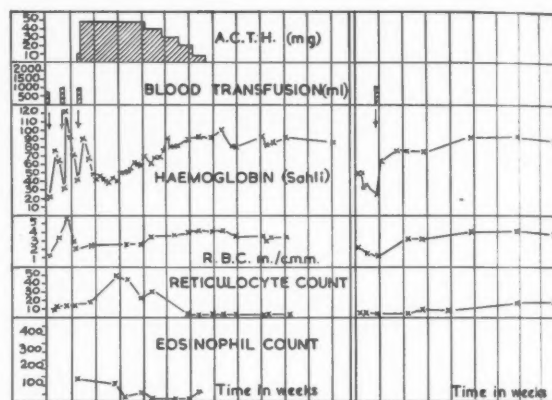
FIG. 2.   FIG. 3.

Case 3. V.P., a girl, aged 8 years, had no relevant personal or family history of previous illness. A sister who had a mild influenzal type of illness at the time of the patient's admission was examined shortly afterwards, and found to be normal. V.P. was admitted with three days' history of fever, lassitude, vomiting and slight epigastric pain. Three hours before admission she was noted to be dyspnoeic and extremely pale. On examination, she was found to be very pale, with slight icterus. She was febrile (103·6° F.) and dyspnoeic, with enlarged soft nodes in the neck, axillae and groins. The spleen was hard and extended three inches below the costal margin. The liver was abnormally firm and was felt one inch below the costal margin. There were a few petechiae in the conjunctivae and palate. The retinae were normal. Findings on physical and radiological examination of the chest were normal. No haemoglobinuria occurred.

The blood count on admission showed: Haemoglobin 50% (Sahli), red cells 2·3 m. per c.mm., colour index 1·09, leucocytes 2,700 per c.mm. (polymorphs 29%, monocytes 12%, lymphocytes 59%).

The haemoglobin dropped to 28% within six days of admission. The blood film showed normal red cell morphology, and there was no evidence of leukaemia. Platelets were normal. Marrow biopsy showed normoblastic hyperplasia. The serum bilirubin level was 1·2

mg. per 100 ml., and the faecal urobilinogen 248 mg. per 100 g. Unfortunately, the original Coombs and serum agglutination tests are not available. There has been no relapse following a single blood transfusion, given on the seventh day after admission, and the child remains well despite persistent hepato-splenomegaly. The direct Coombs test was positive in the eighteenth week of her illness, but subsequently became negative. The early progress and treatment are shown in Fig. 3.

Case 4. J.G., a boy, aged 8 years, had no relevant family or personal history of previous illness. He was admitted with 14 days' history of fever, listlessness and pallor, which had become much worse during the last four days. He had passed dark urine, and had become jaundiced during the two days preceding admission. On examination, he was found to be extremely pale and jaundiced, with moderate enlargement of the spleen, liver and lymph nodes. There was no fever. There were no haemorrhages, and the retinae were normal. Findings in the chest were normal, and subsequent x-ray examination was negative. Gross haemoglobinuria was present during the first three weeks, and again during a relapse in the ninth and tenth weeks.
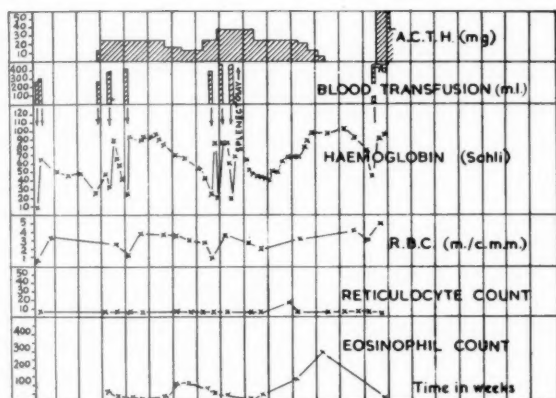

FIG. 4.

The blood count on admission showed: Haemoglobin 19% (Sahli), red cells 1·05 m. per c.mm., colour index 0·93, leucocytes 28,000 per c.mm. (polymorphs 66%, metamyelocytes 3%, myelocytes 1%, monocytes 2%, lymphocytes 28%) and nucleated red cells 117 per 100 white cells.

The blood film showed many haemoglobinized normoblasts, macroreticulocytes and microspherocytes. The platelets were normal. There was no evidence of leukaemia. Marrow biopsy was not performed. The serum bilirubin level was 3·2 mg. per 100 ml., and the faecal urobilinogen was 630 mg. per 100 g. There was gross excess of urobilinogen in the urine. A.C.T.H. was given to this child in view of severe relapses following each of five transfusions. He responded well to A.C.T.H., but relapsed following withdrawal. After three further transfusions had been given splenectomy was performed, but this had no apparent effect on the course of his illness. A second course of A.C.T.H. was therefore given, to

which he again responded. In the seventeenth week after admission cortisone was substituted for A.C.T.H. to enable him to continue treatment at home. One further attempt at withdrawal resulted in brisk haemolysis, and he still requires 75 mg. of cortisone daily, 30 weeks after the beginning of his illness.

The direct Coombs test was repeatedly positive, but became negative during the thirteenth week while he was receiving A.C.T.H. It again became positive during the last relapse, and still has not reverted to negative after 30 weeks. The early progress and treatment are shown in Fig. 4.

Epidemiological Considerations

In view of the comparative rarity of acute acquired haemolytic anaemia, and of its suspected association with infection, it was considered that these cases might represent the effect of an epidemic of some known infective disease. Paul-Bunnell and Widal tests in all four cases were negative. Serum from each case was cultured for virus, with negative results. Agglutination tests for the atypical pneumonia group were carried out by the Central Virus

TABLE

COMPLEMENT FIXATION TESTS

	Influenza		Glandular Fever	Psittacosis L.G.V.	Agglutination Streptococcus M.G.
	A	B			
V.E.	<1/8	<1/8	<1/4	<1/8	<1/10
H.S.	<1/8	<1/8	<1/4	<1/8	1/10
V.P.	<1/8	<1/8	<1/4	<1/8	<1/10
J.G.	<1/8	>1/64	<1/4	<1/8	<1/10
Second specimen		1/32			

Reference Laboratory at Colindale. Apart from the presence of a titre of 1 in 64 in the influenza B complement fixation test in a specimen from J.G., no significant results were obtained. The full results are listed above.

Local enquiries were made from the Medical Officer of Health, the Superintendent of the City Fever Hospital and from the hospitals in the surrounding towns concerning the prevalence of epidemic disease. There was at the time in question no outbreak of virus pneumonia, glandular fever, poliomyelitis, gastro-enteritis, encephalitis or other unidentified illness which might possibly have been related to the dramatic appearance within 16 days of our four cases of acute acquired haemolytic anaemia.

Discussion

In this small group of four cases one child responded after one transfusion only and another after transfusion and A.C.T.H. The two remaining children had the spleens removed and were given

intensive A.C.T.H. therapy. This bears out the difficulty of prognosis in any single case, which is in accordance with the findings of Dameshek and other leading authorities. In Lederer's series (1925, 1930) one patient recovered without transfusion, and the other five with transfusion alone. Dameshek and Schwartz (1940) reviewed about 100 cases, in 66 of which transfusions had been carried out. In 22 of these cases transfusion alone failed to control the haemolysis. They showed that recovery occurred following splenectomy in 20 of 23 cases operated on, 18 of which had been transfused previously without success.

In view of the fact that Dameshek and Rosenthal (1951) obtained satisfactory control of the haemolytic process with A.C.T.H. in certain cases of acute leukaemia, they extended the trial to cases of acute acquired haemolytic anaemia which had failed to respond to transfusion. Ten cases were treated, and of these nine responded satisfactorily. The further reports on this method of treatment which have appeared in the last two years have continued to be favourable, and Dameshek (1952) is now able to report 22 cases, with complete haematological and clinical control in 14 and improvement in six.

Unfortunately, it is necessary to use relatively large doses of A.C.T.H. in these cases (Dameshek and Rosenthal, 1951) and in children, the subject of this paper, it has been difficult to achieve adequate therapeutic dosage without producing toxic effects. In spite of clinical toxic effects, such as undue gain in weight and glycosuria, there was no biochemical or electrocardiographic evidence of electrolyte disturbance. A reliable method of assessing the degree of control of the haemolytic process is required, especially during the period of withdrawal. In view of the very rapid fall in haemoglobin concentration in these children, we found that routine blood counts did not give warning of relapse in time to reinstitute larger dosage before transfusion became necessary. Despite the fact that Clearkin (1952) does not find the Coombs test a reliable guide, we decided to use daily direct Coombs tests in an effort to anticipate acceleration of the haemolytic process. Consideration was given to the possible advantages of the indirect method, but the necessary facilities were not available at the time.

In the two cases which relapsed during the withdrawal period it was decided to resort to splenectomy in view of the large doses of A.C.T.H. which were required, the long duration of the illness, and the necessity for repeated blood transfusions. The operation in each case was performed by Professor D. Chamberlain. Of these two children, V.E. appeared to recover after splenectomy, undertaken

during the second course of A.C.T.H., but relapsed on withdrawal of the drug. She subsequently responded to intramuscular cortisone. The other child, J.G., was operated on during a relapse, but failed to maintain a satisfactory haemoglobin level. A further course of A.C.T.H. was successful in controlling the haemolysis, but the Coombs test has remained positive, and it has been necessary to continue therapy with oral cortisone.

Summary

Four cases of acute acquired haemolytic anaemia in children which presented within a period of 16 days are described, and the possibility of an infective basis for this condition is discussed. The children ranged in age from 6 months to 8 years.

The effects of treatment with A.C.T.H. on the course of the disease are shown, and afford evidence that the underlying abnormal antibody reaction can be controlled if relatively large doses are given.

The place of blood transfusion, splenectomy and A.C.T.H. therapy in clinical management is discussed.

The variable course and progress of the disease, and the need for an individual approach to cases are stressed.

REFERENCES

Best, W. R., Limarzi, L. R. and Poncher, H. G. (1951). *J. Amer. med. Ass.*, **147**, 827.
Chauffard, A., Troisier, J. and Vincent, C. (1908). *Sem. méd., B. Aires*, **28**, 345.
Clearkin, K. P. (1952). *Lancet*, **1**, 183.
Crary, H. I. and Beck, I. A. (1952). *Ann. intern. Med.*, **36**, 1106.
Dacie, J. V. and Gruchy, G. C. de. (1951). *J. clin. Path.*, **4**, 253.
Dameshek, W. (1950). *Blood*, **5**, 791.
—— (1952). *Brit. med. J.*, **2**, 612.
—— and Rosenthal, M. C. (1951). *Med. Clin., N. Amer.*, **35**, 1423.
—— and Schwartz, L. I. (1951). *New Engl. J. Med.*, **244**, 117.
—— and Schwartz, S. O. (1940). *Medicine, Baltimore*, **19**, 231.
Davidson, L. S. P., Duthie, J. J. R., Girdwood, R. H. and Sinclair, R. J. G. (1951). *Brit. med. J.*, **1**, 657.
Etess, A. D., Bassen, F., Litwins, J. and Sussman, L. N. (1951). *Acta haemat., Basel*, **6**, 105.
Gardner, F. H. (1950). *Blood*, **5**, 791.
——, McElfresh, A. E., Harris, J. W. and Diamond, L. K. (1951). *J. Lab. clin. Med.*, **37**, 444.
Hagberg, B. (1952). *Acta Soc. Med. upsalien*, **56**, 273.
Hayem, G. (1908). *Bull. Soc. méd. Hôp., Paris*, **25**, 122.
Langeron, L. (1951). *Ibid.*, **67**, 488.
—— (1925). *Ibid.*, **170**, 500.
Lederer, M. (1930). *Amer. J. med. Sci.*, **179**, 228.
Ley, A. B. and Gardner, F. H. (1951). *J. clin. Invest.*, **30**, 656.
Mallarmé, J., Martin, Eyquem, Fleury (1951). *Sang.*, **22**, 580.
Meyer, J. F. (1951). *Amer. J. Dis. Child.*, **82**, 721.
Rosenthal, M. C., Spaet, T. H., Goldenberg, H. and Dameshek, W. (1952). *Lancet*, **1**, 1135.
Unger, L. J. (1951). *Amer. J. clin. Path.*, **21**, 456.
Widal, F., Abrami, P. and Brulé, M. (1907). *Presse méd.*, **15**, 641.
Young, L. E., Christian, R. M. and Izzo, M. J. (1951). *Med. Clin. N. Amer.*, **35**, 571.

TWO CASES OF CONGENITAL MITRAL STENOSIS TREATED BY VALVOTOMY

BY

B. D. BOWER, J. W. GERRARD, A. L. D'ABREU and C. G. PARSONS

From the Children's Hospital, Birmingham

Congenital mitral stenosis is rare but its accurate diagnosis is more than an academic exercise since surgical relief may now be possible.

It is usually associated with anomalies of the septa and great vessels and hypoplasia of the left ventricle and aorta, a combination of defects usually attributed to unequal division of the common atrio-ventricular canal (Rokitansky, 1875, quoted by Brown, 1939; Abbott, 1927). Patent ductus arteriosus, atrial or ventricular septal defects, or co-arctation of the aorta may accompany these anomalies. Death usually occurs within the first few days or weeks of life. The necropsy records of the Birmingham Children's Hospital for the years 1940 to 1951 inclusive contain 198 examples of congenital heart disease. Mitral stenosis or atresia which, because of co-existent left ventricular and/or aortic hypoplasia was considered to be due to unequal division of the atrio-ventricular canal, was observed on 15 occasions. The patients survived from one hour to two years eight months; 12 died within the first six weeks of life.

Much more rarely, however, mitral stenosis occurs without any other associated anomaly. One possible example was found in this necropsy series, the child living for six months. This type of case is important since successful valvotomy should add many years to the patient's life. We describe two cases, which we believe are the first in which valvotomy has been performed.

Case Reports

Case 1. This patient, a girl, was aged 5½ years at operation.

Pregnancy and birth were normal. Shortly after birth she was said to have signs of congenital heart disease. From the age of 9 months to 3½ years, when she was first seen at this hospital, she had repeated attacks of bronchitis and pneumonia. Her exercise tolerance was moderately impaired but there was no history of cyanosis or squatting. One of her four siblings has a patent ductus arteriosus. There is no history of rheumatic infection in the patient or her family. At the age of 3½ years she was 10 lb. under weight. There was no cyanosis or clubbing. The heart was not enlarged and at the apex there was a widespread diastolic thrill and a long diastolic murmur ending with a crescendo effect in a slapping first sound. The pulmonary second sound was accentuated.

INVESTIGATIONS. Radiographs showed a slightly enlarged heart with some pulmonary congestion. There was no evidence of left ventricular hypoplasia in the left oblique view.

An E.C.G. showed a suggestion of right ventricular preponderance with a broad and abnormal P wave in all leads (Fig. 1).

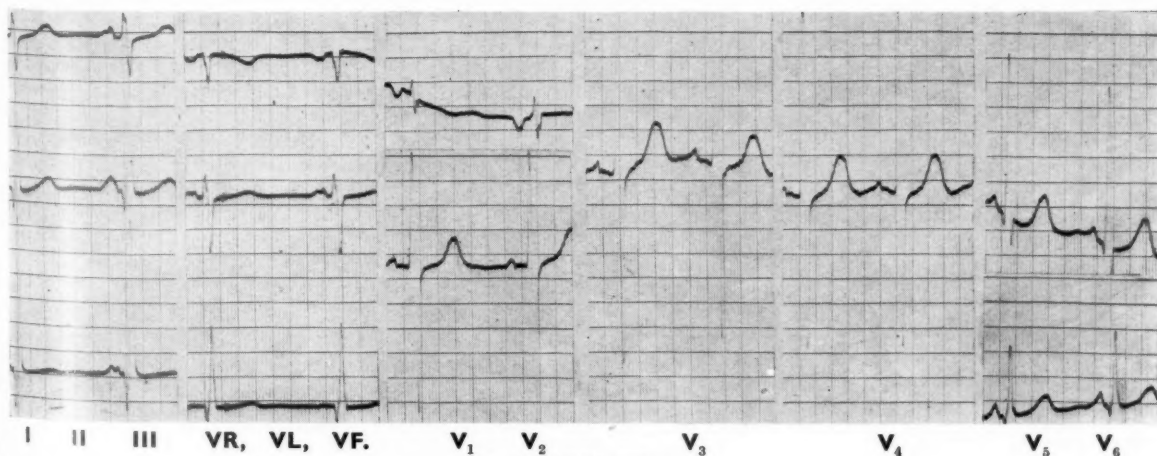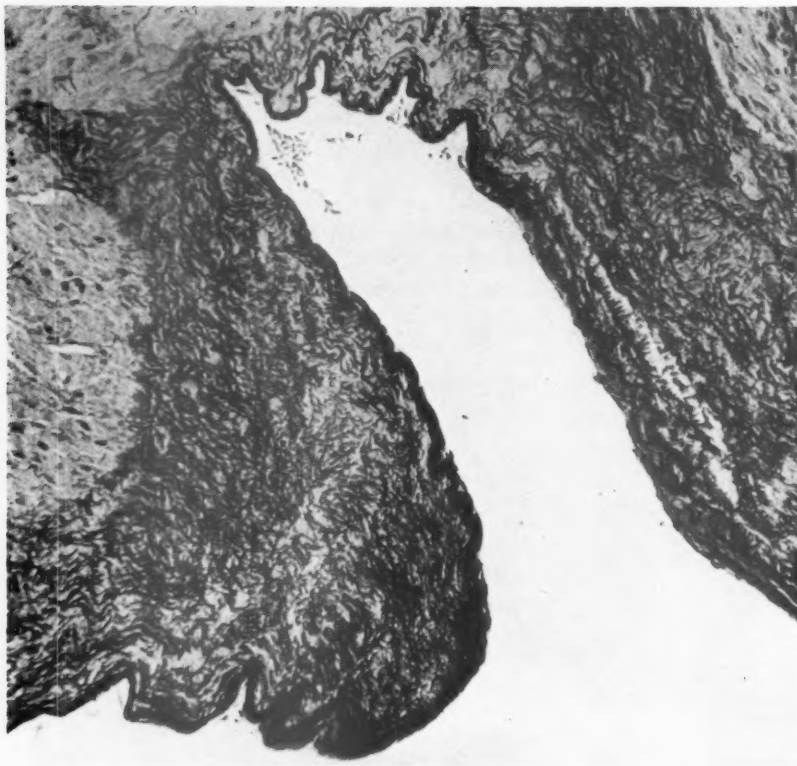I   II   III   VR, VL, VF.   V₁   V₂   V₃   V₄   V₅   V₆

FIG. 1.—E.C.G. of Case 1.

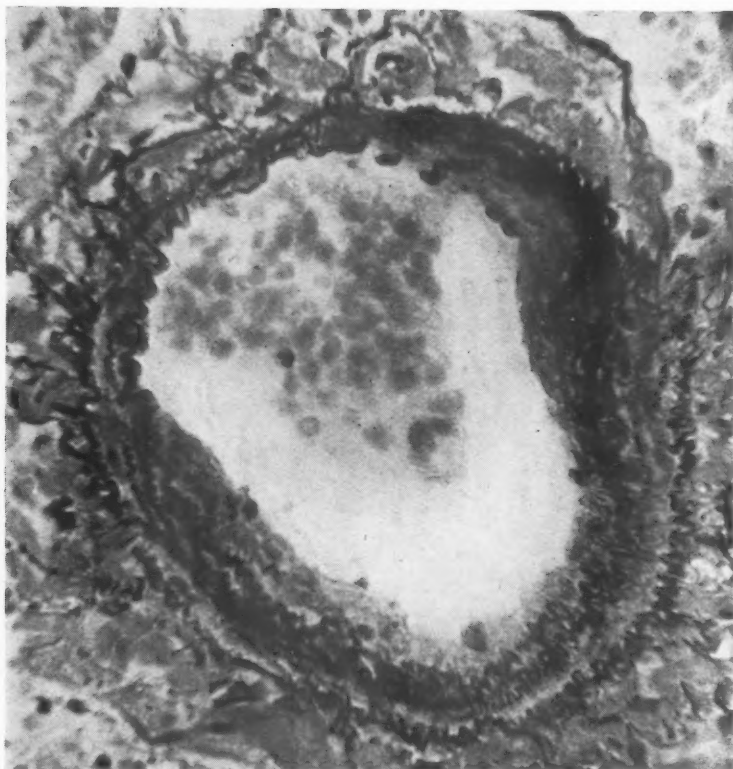FIG. 2.—Section of left auricle showing fibro-elastosis of the endocardium (Weigert elastica, van Gieson ×120).

FIG. 3.—Section of lung showing the changes in a branch of the pulmonary artery (Weigert elastica, van Gieson ×220).

Angiocardiography. The diodone entered the descending arch of the aorta from the right ventricle and later in the series the ascending aorta was filled from the left ventricle in the usual manner. The left heart chambers were large. It seemed probable that mitral stenosis might have raised the pulmonary artery pressure sufficiently to reverse the flow in a patent ductus arteriosus. (This was confirmed by the fact that after this procedure the feet were more cyanosed than the hands whereas no difference had been observed previously.)

Cardiac catheterization performed seven months later showed the pressure in the right ventricle to be extraordinarily high (i.e. 58 cm. of water above the table top) as it was in the pulmonary artery, and there was increased oxygen saturation in the pulmonary artery. These findings supported the diagnosis but suggested that the flow in the ductus was now in the usual direction (aorta to pulmonary artery).

As her condition had deteriorated since her first examination at the age of $3\frac{1}{2}$ years, thoracotomy was performed by one of us (A.L.d'A.). It was argued that if pulmonary artery pressure, as measured by direct insertion of a needle, fell during temporary occlusion of the ductus then the ductus should be interrupted, as the flow must be in the usual direction. If this did not occur, then the flow must be from pulmonary artery to aorta and mitral valvotomy should be proceeded with as the only way of reducing the pulmonary hypertension. The transient attacks of cyanosis were accepted as evidence that periodic reversal of blood flow through the ductus did occur.

OPERATION. This was performed on January 17, 1952.

The anaesthetic used was pentothal, curare, and oxygen delivered through an intra-tracheal tube. The left chest was opened through the classical posterior lateral thoracotomy, the pleura being opened through the bed of the resected fourth rib. The left lung was grossly plethoric and heavy and the lymphatic nodes of the mediastinum were dark resembling those seen in some adult patients with mitral stenosis associated with haemosiderosis of the lung. The ductus arteriosus was exposed in the usual way. It was very large and clearly formed a big channel between the aorta and the pulmonary artery. There was no thrill palpable and this in itself was regarded as an indication of reversal of flow through a wide channel. After the ductus had been fully exposed a needle was inserted into its lumen and a pressure of over 145 cm. of saline recorded on the manometer. With the needle still in place the ductus was temporarily occluded and the pressure, if anything, rose. The reversed flow was obviously acting as a protective mechanism and ligation of the ductus was contra-indicated. The pericardium in front of the left phrenic nerve was opened widely. The auricular appendage of the left atrium was distended and, in spite of the age of the child, was readily occluded by Brock's clamp. An incision was made in the appendage sufficiently large to admit the index finger. The clamp was opened and the mitral valve explored digitally. The valve orifice was the size of a pencil and no commissures could be felt. The whole valve area was firm and in no way resembled that encountered in adult

mitral stenosis. With considerable difficulty the valve was split and the index finger could then enter the left ventricle comparatively easily. The auricular wound was closed with interrupted fine thread sutures and the clamp removed. The pericardium was loosely closed and the thoracic wound closed with interrupted thread sutures without drainage.

The child stood the operative intervention very satisfactorily and left the table with a blood pressure the same as that recorded before the operation.

At operation a biopsy was done of the left lung and the left atrium.

BIOPSY EXAMINATIONS. The following are recorded.

Left Atrium. There was marked infiltration of sub-epicardial connective tissue with lymphocytes, polymorphonuclear leucocytes and plasma cells, which extended into the interstitial tissue of the outer part of the myocardium. The endocardium was very thick due to numerous layers of elastic fibres and less numerous collagenous fibres (Fig. 2).

Lung. There was partial collapse, and heart failure cells were present in the alveoli. There was oedema and moderate mononuclear infiltration of the interalveolar septa. Myoelastic hypertrophy of the small branches of the pulmonary artery was present, with cushion-like proliferation of the subendothelial intimal tissue (Fig. 3).

FOLLOW-UP. Seven months after operation her exercise tolerance has greatly increased. Her cardiac signs have varied. At times a rough presystolic murmur with a slapping first sound has been present, and at other times there have been a murmur and thrill occupying the whole of diastole. A ductus murmur has been heard occasionally. Her feet are sometimes a little more cyanotic than the hands showing that at times the pulmonary artery pressure exceeds the aortic.

Cardiac catheterization four months after operation showed a pulmonary artery pressure of 128 cm. of saline above the table top and an oxygen saturation greater in the pulmonary artery than in the right ventricle. There was, therefore, still gross pulmonary hypertension, and the shunt on that occasion seemed to be from the aorta to the pulmonary artery.

Case 2. This was a boy aged $9\frac{1}{2}$ months at operation. Pregnancy and birth were normal (birth weight 5 lb. 1 oz.). He was admitted to the Children's Hospital, Birmingham, on February 14, 1952, aged 7 months. For the previous six weeks he had not taken his feeds, had failed to gain weight, and had had a slight cough. He was a pale, somewhat wasted, fretful baby, weighing 10 lb. 8 oz., but he was not cyanosed or dyspnoeic. The heart was enlarged and a presystolic thrill and rough crescendo murmur followed by a soft systolic murmur were heard. The heart sounds seemed normal, but on later occasions the mitral first sound was slapping in character. The liver and spleen were enlarged and there were inspiratory crepitations at the base of the left lung.

He became dyspnoeic after admission and his respiratory rate rose. Accordingly 'digoxin' was started on the fifth day, with initial improvement. A week later, however, he again deteriorated and showed signs of left- and right-sided cardiac failure. Aminophylline, mersalyl,

and 'papaveretum' were given in addition to the 'digoxin' and he again improved within the next 24 hours. For the next two weeks he remained in mild respiratory distress

I, II, III, VR, VL, VF V₁ V₂ V₄ V₆

FIG. 4.—E.C.G. of Case 2.

but without clinical evidence of cardiac failure, and it was possible to perform angiocardiography and cardiac catheterization during this time. He then had a second attack of cardiac failure despite continued treatment.

INVESTIGATIONS. A radiograph on admission showed an enlarged heart with vascular engorgement of both lung fields spreading out from the hila, more marked on the right.

An E.C.G. showed right ventricular preponderance and an abnormal P wave in all leads (Fig. 4).

Cardiac Catheterization. There appeared to be either a very large right atrium or else a large atrial septal defect because of the distance through which the catheter tip could be moved transversely, but the oxygen contents of the samples of blood obtained with the catheter tip at the two limits of its excursion were the same. The abnormality was therefore assumed to be a large right atrium.

Site	O₂ Content (vol. %)	
Inferior vena cava	9·9	
Right atrium ..	(R) 8·89	(L) 8·65
Right ventricle ..	8·7	

There was thus no evidence of a left-to-right shunt.

Angiocardiography. This showed a normal circulatory route, but there was a remarkable hold-up of diodone in the left atrium. This chamber appeared rather large, and the left ventricle was not seen adequately filled in any of the pictures (Fig. 5).

As these findings supported the diagnosis and, as he had had two attacks of failure while fully digitalized, it was decided that mitral valvotomy should be attempted.

OPERATION (A.L.d'A.). On May 1 under pentothal, curare and intra-tracheal oxygen anaesthesia, the left chest was widely opened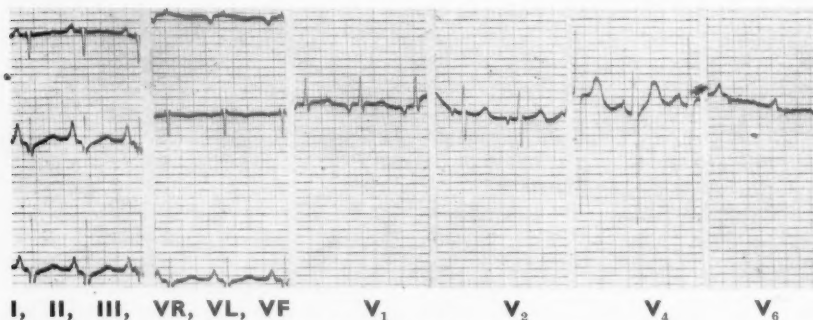 through the bed of the resected fifth rib. The pericardial sac, which contained an excessive amount of fluid, was opened in front of the left phrenic nerve. The left atrium and its appendage were grossly distended. The right ventricle was greatly dilated and appeared to be almost aneurysmal towards its apex. The left pulmonary artery was enlarged and the aorta smaller than usual though by no means hypoplastic. The pressure in the pulmonary artery was recorded by means of a saline manometer and was over 85 cm. of saline. The left auricular appendage was held loosely in an atrial clamp and a small incision made into it through which Brock's pulmonary valve probe was passed. This was guided into a small hole in the mitral valve. The probe completely blocked the orifice and was withdrawn rapidly when the heart began to fail. Brock's small size pulmonary valvulotome was then passed through the valve which cut readily. During this procedure the heart beat became irregular but normal rhythm recurred after a few minutes when the lungs had been fully oxygenated by the anaesthetist exerting pressure on the anaesthetic bag. The opening in the valve was then dilated by Brock's dilators and the atrial incision closed by interrupted thread sutures. The pericardium and the chest were closed in the usual way with interrupted thread sutures without drainage.
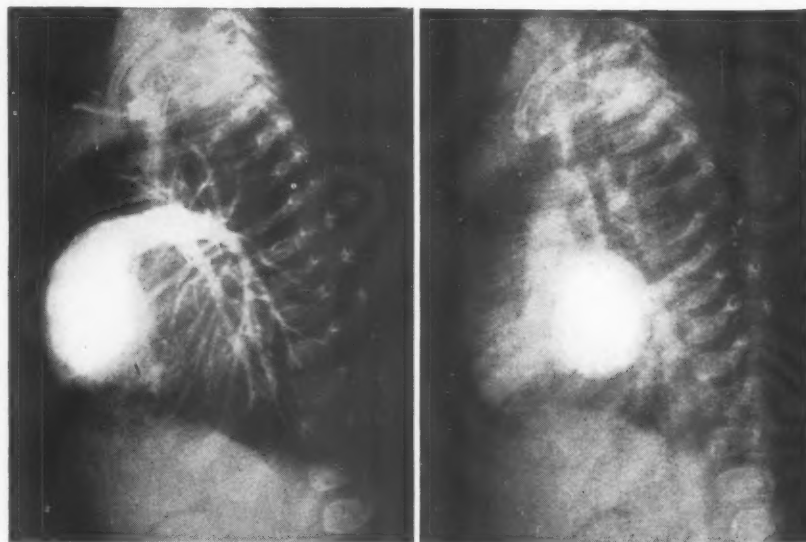

FIG. 5.—Angiocardiogram: (*a*) 1·7 seconds, showing filling of the right ventricle and branches of the pulmonary artery: (*b*) 7·1 seconds showing filling of the dilated left auricle and the whole of the aorta and common iliac arteries, but no dye in the left ventricle.

The child's immediate post-operative condition was very satisfactory; the colour remained good. The infant remained in good condition for 36 hours but during a feed, choked, collapsed suddenly and died.

to patches of chondroid connective tissue. There were no increase in elastic fibres and no inflammatory changes. The endocardium of the right ventricle was normal, but that of the left ventricle showed patchy thickening

FIG. 6.   FIG. 7.

FIGS. 6 and 7.—Left auricle and left ventricle opened to show the mitral stenosis (free edge of mitral valve arrowed in Fig. 7) and the fibro-elastosis of the left auricle.

NECROPSY (Dr. H. S. Baar). There were no abnormalities outside the cardiovascular and respiratory systems.

The heart was markedly enlarged (weight 56 g.; normal for age, 38 g.). There was eccentric hypertrophy of the right ventricle but the left ventricle was normal in size and its wall was of normal thickness. The maximum thickness of the walls of both ventricles was 7 mm. The cusps of the mitral valve were fused, the aperture only admitting a thin pencil (approximately 5 mm. in diameter). In one place, in the middle of the posterior part of the valve, there was a recent incision 3 mm. in length. The valve itself was thick, hard, nodular and white. There was marked endocardial fibro-elastosis affecting the whole of the left atrium, the cranial part of the left ventricle and, to a lesser degree, the right atrium (mainly on the inter-atrial septum). The tricuspid, pulmonary and aortic valves were normal and the origins of the coronary arteries were normally situated. The position and size of the great vessels were normal and there was no patency of the septa. There were sutures in the wall of the left auricle (Figs. 6 and 7).

There were extensive areas of atelectasis in the lungs, particularly in the left lower lobe. There were also increased marking of the interstitial tissue and some areas suggestive of carnification.

The mediastinal lymph nodes were enlarged, those at the tracheal bifurcation being about 1 cm. in diameter. They were soft and greyish-red.

Histology. The thickening of the mitral valve was due

due mainly to numerous layers of elastic fibres with a few collagenous fibres between them.

The capillaries of the interalveolar septa were distended and engorged. There was partial collapse. The alveoli and alveolar ducts contained macrophages, many of which, if not all, gave a positive Prussian blue reaction (Fig. 8).
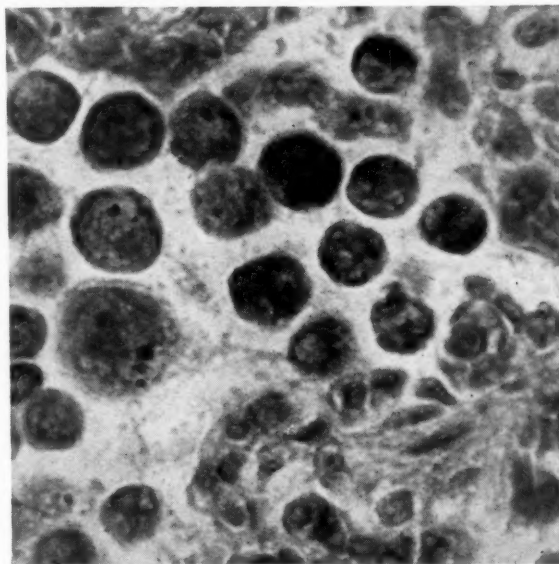

FIG. 8.—Section of lung showing heart failure cells (Prussian blue, ×480).

There was moderate myoelastic hypertrophy of the small branches of the pulmonary artery, but no intimal proliferation.

Congestion and centrilobular fatty degeneration of the liver were present.

Case 3. Since these cases were reported a further case of isolated mitral stenosis has come to necropsy at this hospital. Death occurred before the diagnosis could be made, and so valvotomy was not performed. The baby was aged 2 months. The necropsy findings were very similar to those in case 2: fibro-elastosis of the left atrium was present. The mitral valve, although stenosed, showed no evidence of inflammation.

Discussion

Aetiology. It seems clear that when mitral stenosis is associated with other gross cardiac defects the cause is mal-development of the primitive heart during the first trimester of intra-uterine life (Emery and Illingworth, 1951). Unequal division of the common atrio-ventricular canal is the probable cause. The time when this mal-development occurs, and possibly its extent, determines the degree of mitral stenosis or atresia and the presence or absence of septal defects and abnormalities of the great vessels. 'Atresia' denotes non-development, and 'stenosis' normal development with fusion of the valve cusps, but intermediate stages occur and the terms clearly overlap (Brown, 1939).

When mitral stenosis occurs as an isolated lesion the cause is less certain, and controversy has been acute on this point. The usual cause which was advanced until recent years was foetal endocarditis (Day, 1932; Eigen, 1938; Johnson and Lewes, 1945; McConnell, 1950) and indeed the pathological findings are often similar to those of healed endocarditis. Gross (1941), however, in an exhaustive review of the literature could find no evidence that foetal endocarditis caused any cardiac lesions and gave his own reasons for considering a congenital origin more likely: he pointed out first that in previously reported cases histological examination had not often been performed and that when this had been done the acute stage had never been seen, and secondly that maternal disease had only rarely occurred during pregnancy. The changes usually seen are endocardial fibrosis, extending often as strands into the myocardium; occasionally calcification of the valve; lymphocytes and Aschoff bodies do not occur. He postulated a primary hyperplasia of the endocardial elastic tissue, perhaps causing secondary infarction of the sub-endocardial muscles supplied by arterio-luminal, arterio-sinusoidal and Thebesian vessels. This pathological appearance, now known as fibro-elastosis, has usually been present in the reported cases of mitral stenosis, both with and without other cardiac defects (Day, 1932; Farber and Hubbard, 1933; Johnson and Lewes, 1945; Gross, 1941; Emery and Illingworth, 1951; Blumberg and Lyon, 1952; Johnson, 1952). Some of the authors consider this to be evidence of foetal endocarditis. It certainly occurred in one and probably in both of the cases discussed in this paper and also in nine of the 15 cases of mitral stenosis or atresia of the 'unequal division' type mentioned above. We agree with Gross. If an error of development is indeed the cause in the latter type of case, then 'pure' mitral stenosis is also probably due to this, since fibro-elastosis is common to both. As in most reported cases there were no Aschoff bodies or other evidence of acute rheumatism in the two cases reported here. It is difficult for two other reasons to explain our case 2 on the theory of endocarditis. There is no history of a rheumatic episode in mother or child and, even if a silent rheumatic affection in the mother is assumed, acquired mitral stenosis could not have developed in that time, if the usual minimum time of two or three years is accepted.

Johnson (1952) also rejects foetal endocarditis as a cause of mitral stenosis and fibro-elastosis and postulates anoxia of the endocardium due to (1) coronary artery anomalies, (2) premature closure of the foramen ovale, which would prevent oxygenated blood from entering the left auricle and ventricle, or (3) valvular atresias, from which stagnation anoxia would develop. This theory is attractive, as it explains the more frequent occurrence of the condition on the left side of the heart, since the second mechanism would operate only on the left, while the others would operate equally on the two sides. The author even suggests that when there is premature closure of the foramen ovale the resulting thickening of the endocardium may prevent normal growth of the muscle wall and thus explains the occurrence of left ventricular and aortic hypoplasia in some cases. This explanation, however, cannot displace the 'unequal division' theory, for in some cases of mitral stenosis with a hypoplastic left ventricle and aorta, there is no fibro-elastosis.

Diagnosis. The history in both cases was suggestive, i.e. recurrent pulmonary infections, dyspnoea, and in one case congestive heart failure; physical examination confirmed the diagnosis by the discovery of a classical presystolic murmur and accentuated slapping first sound. These signs, however, were variable and there were times when the diagnosis seemed certain on clinical grounds and other times when it was doubtful.

Investigations were not as helpful as might have been hoped. There was no significant direct radiological enlargement of the left auricle. An E.C.G.

showed right ventricular preponderance, which is usual at this age, but it did also show a broad and abnormal P wave in both cases. Cardiac catheterization did not help directly but it excluded septal defects, and confirmed the presence of a silent ductus in case 1, besides showing extreme pulmonary hypertension in both cases. Angiocardiography, which is not usually regarded as of great value in the diagnosis of mitral stenosis, was useful in case 2 by showing a large left atrium with stasis lasting several seconds, and in case 1 by showing the ductus and the direction of its blood flow.

Selection of Cases for Operation. Congenital mitral stenosis is theoretically the ideal type of case for mitral valvotomy, provided the left ventricle and aorta are normally developed, for cardiac embarrassment is due entirely to the mechanical obstruction and the common contra-indications to operation in the acquired form, namely previous myocardial damage and active infection, are absent. It is important, therefore, to differentiate the type of case with 'pure' mitral stenosis from the 'unequal division' type, for only the former is likely to benefit from the operation. The facilitation of blood flow into the left ventricle is pointless if the aorta is not large enough to receive it. We took the presence of a slapping first sound as evidence of a normal left ventricle. Angiocardiography did not show the size of the chamber, but in case 2 a normal aorta was demonstrated. In case 1 neither left ventricle nor aorta could be demonstrated because of the by-pass. In the absence of definite proof of the diagnosis we think thoracotomy is justifiable if there are signs of pulmonary hypertension or a history of attacks of congestive cardiac failure. It is, of course, impossible at present to make any statement about prognosis after valvotomy but it seems fairly certain that death occurs usually before the age of 5 years without surgery. Secondary change in the pulmonary arterial tree may, however, cause pulmonary hypertension to continue, and thus limit improvement. The problem of the length of time which elapses before pulmonary arterial changes make pulmonary hypertension permanent is at present occupying the minds of cardiologists working with cases of acquired mitral stenosis, and is just as important in the congenital type. It was disturbing to see changes in the branches of the pulmonary artery in case 2 at the age of 9 months. Case 1 only improved slowly after operation, and it is far too early to assess its result.

The Surgical Problems. From the necropsy experience quoted it would seem that most children will require surgery before the age of 5; it is, however, important to note that the auricular appendage of one child of 5 was sufficiently capacious to allow a digital examination of the stenosed valve to be carried out. This clearly would be impossible in the case of children under the age of 3 or 4 and surgical attempts at commissurotomy would have to be made blindly by passing a valvulotome through a small incision in the auricular appendage; such a method can never be so accurate or precise as that following a digital exploration, but the experience described in case 2 shows that the operation is possible. The division of the stenosed valve by a knife cannot be placed accurately through the antero-lateral and postero-lateral commissures as in adult mitral stenosis, but this may not be so important in congenital stenosis where there is no sign of properly developed cusps and the condition is more akin to that of pulmonary valvular stenosis: the risk of regurgitation following must be accepted and a certain degree of this would be preferable to a tight stenosis. Both these young hearts stood the surgical intervention extremely well.

Summary

Two cases of congenital mitral stenosis, one with no other abnormality and the other with a co-existent patent ductus arteriosus, are described. The diagnosis was confirmed at operation and, in one case, also at necropsy.

Mitral valvotomy was performed in both cases.

Clinical diagnosis may be easy at times but difficult at others. Confirmation may be difficult.

The selection of suitable cases is important since valvotomy should help the case with a good left ventricle but could not help the commoner case due to unequal division of the common atrio-ventricular canal.

REFERENCES

Abbott, M. E. (1927). In Osler's *Modern Medicine*, 3rd ed., vol. IV, p. 754. London.
Blumberg R. W. and Lyon, R. A. (1952). *Amer. J. Dis. Child.*, **84**, 291.
Brown, J. W. (1939). *Congenital Heart Disease*. London.
Day, H. B. (1932). *Lancet*, **1**, 1144.
Eigen, L. A. (1938). *Amer. Heart J.*, **16**, 363.
Emery, J. L. and Illingworth, R. S. (1951). *Archives of Disease in Childhood*, **26**, 304.
Farber, S. and Hubbard, J. (1933). *Amer. J. med. Sci.*, **186**, 705.
Gross, P. (1941). *Arch. Path., Chicago*, **31**, 163.
Johnson, F. R. (1952). *Ibid.*, **54**, 237.
Johnson, R. S. and Lewes, D. (1945). *Brit. Heart J.*, **7**, 52.
McConnell, B. E. (1950). *Archives of Disease in Childhood*, **25**, 186.

ECTOPIC OSSIFICATION IN TUBERCULOUS MENINGITIS

BY

JOHN LORBER

From the Department of Child Health, University of Sheffield

The syndrome of severe wasting, opisthotonus and paraplegia in flexion associated with considerable hydrocephalus is well known to those treating advanced cases of tuberculous meningitis. Once such a condition has developed, the outlook is generally poor. Many patients will die and the survivors will often be handicapped by a variety of physical and mental sequelae.

The purpose of this paper is to describe and discuss a serious complication of tuberculous meningitis which does not seem to have been described before. This consists of ectopic ossification. It only occurred in children with spinal block and paraplegia. During 1950 and 1951 the Tuberculous Meningitis Unit of the Department of Child Health in Sheffield admitted 10 children who developed paraplegia and survived for a minimum period of three months. Ectopic ossification was observed in five of these 10 children, four of whom survived and are alive 16 to 33 months after the onset of meningitis.

Case Histories

In the first patient ectopic ossification was an accidental discovery. A 2-year-old boy had been unconscious for several weeks when gradually increasing difficulty was experienced in flexing him adequately for lumbar punctures. After he regained consciousness the hips were noted to be very stiff. The left thigh was held in flexion, adduction and internal rotation, and the right in flexion and abduction. A radiograph of the pelvis three months after admission confirmed the suspected tuberculosis of the left hip joint with ankylosis, but the right hip joint itself was normal. The soft tissues surrounding both hip joints presented a most unusual appearance. There were extensive, ill-defined opacities, which appeared to be deposits of calcium (Fig. 1), situated in the adductors and flexors.

On orthopaedic advice no active measures were taken. The masses of ectopic calcifications or ossifications increased, leading to almost complete fixation of both hip joints in unfavourable positions. By now the child was well enough to stand and even walk with difficulty, but was unable to sit. He recovered from the meningitis, was transferred to an orthopaedic hospital, and he is still there, nearly three years after his original admission. By November, 1950, 10 months after admission, a massive bony bar was felt in the right thigh. A radiograph at this stage showed more clearly the extent and location of the lesions. On the right side the ossification involved the psoas major, the adductor longus, the adductor magnus and the pectineus (Fig. 2). The distribution on the left could not be so accurately determined because of the associated tuberculous arthritis with ankylosis.

Between February, 1951, and January, 1952, he underwent three operations. At the first the alignment of the left femur was corrected by an osteotomy. At the same time a mass of new bone was located, mainly in the iliacus, and was removed. It was separate from the femur. Unfortunately further new bone was again deposited and fixed the neck of the femur to the ilium.

The second operation was designed to remove the ectopic bone from the right thigh. Large masses of bone were removed from the adductors. After this considerable movement was possible in the hip joint, although deeper masses of bone in postero-medial relation to the hip joint were left in position. No benefit resulted from this operation, because further new bone was deposited and fixed the hip as much as ever. At the third and last operation further new bone was removed from the right thigh, but this procedure made things even worse. Although no new bone was now present in the more distal parts of the thigh, a dense scaffolding of new bone joined the whole of the neck of the femur to the pelvis (Fig. 3).

Although at present the child is in excellent physical and mental health, he is severely disabled; as he cannot sit, he walks with stiff hips and he has developed a scoliosis. There is no movement in the left hip and only some 15 to 20 degrees of flexion and no other movement in the right. In this child operative procedures probably did more harm than good.

In the three other survivors the results are not as serious. One of them is a 2-year-old hydrocephalic ament and ossification in the right adductors is only a curious incidental finding. In the third child metastatic ossification was first detected six months after the onset of meningitis and appeared to be confined to the tendon of the right iliopsoas (Fig. 4). It increased in density and thickness for a further six months (Fig. 5). during which time she remained unconscious. Since then she has made considerable improvement and now, at the age of 4½ years, although still considerably retarded, she can say a few words, she feeds herself and walks with assistance. At the end of September, 1952, there was some radiological evidence of resorption of the heterotopic bone

(Fig. 6). Abduction of the thigh was restricted to some 10 degrees, but flexion and extension were not limited.

The fourth child is now a healthy normal boy of 7. The first evidence of bilateral and symmetrical ossifications was found four months after he developed meningitis. The ossifications appeared to affect the iliopsoas tendons below the level of the pelvis and increased in extent for a further three months (Fig. 7). He recovered and started to walk. His gait was stiff at first, but it is now normal and he has no disability. The ossifications are now both shorter and more slender, suggesting spontaneous absorption of the new bone (Fig. 8).

The fifth child was a girl of 12 who died after a prolonged illness lasting for nearly two-and-a-half years. In the first 18 months she was fully conscious and in good general condition, but in January, 1951, she became much worse. At that time radiographs of the hips as well as of other joints were negative. These were taken because she complained of severe and widespread pain and stiffness in the joints, which were tender. Within a month she developed generalized rigidity, and was barely able to move. A month later bilateral ossifications developed in both iliopsoas muscles and tendons but nowhere else (Fig. 9). Following treatment with intrathecal tuberculin she made a substantial general improvement but the ossifications in the thighs increased greatly (Fig. 10), resulting in complete fixity of the hip joints, which lasted for several months, until her death. She died after a final relapse of meningitis, and at necropsy vast masses of ectopic bone were found both radiologically and by dissection (Fig. 11). The ectopic bone was mainly in the iliopsoas region. There was no evidence of tuberculous arthritis.

Biochemical estimations of serum calcium, phosphorus and phosphatase were normal in every case.

Histological examinations were performed on the specimens of bone removed at operations in the first child and on the necropsy specimens in the last. The presence of bone containing normal bone marrow was demonstrated (Figs. 12 and 13).

Discussion

Since the end of the 1914-18 war the syndrome of metastatic ossification following traumatic paraplegia due to spinal cord injuries has become well recognized. The first detailed account of the condition was given by Dejerine, Ceillier and Dejerine in 1919 on a large series of patients. They treated 160 patients with post-traumatic paraplegia and 78 of these (48·7%) developed metastatic ossifications. In all cases the new bone was deposited in the thigh, either around the hip joint or along the medial condyle of the femur. They never found lesions above the pelvis or below the knee and their observations on this point were confirmed by all subsequent writers on this subject. The joints themselves were not involved. They found no evidence of infection or of haemorrhage in the affected areas, and they found no calcification or ossification in the chronic pressure

sores in these patients. Biopsy specimens of the ectopic ossifications proved the deposits to be normal bone.

Several confirmatory studies have been published but little new has been added to our knowledge. The incidence in some of the larger series (Miller and O'Neill, 1949) has not been as high as that of Dejerine's series. All writers agreed about the characteristic distribution of the lesions, which usually developed within a year after the spinal cord injury. The earliest appearance was usually unknown in the absence of serial radiological studies (Abramson and Kamberg, 1949; Geldmacher, 1925; Hanke, 1943; Heilbrun and Kuhn, 1947; Lüdeke, 1950; Miller and O'Neill, 1949; Soule, 1945; Soule and Stiff, 1949; Stanger, 1947).

Voss (1937) collected from the literature several single cases in which other diseases of the central nervous system were associated with metastatic ossification and added four cases of his own. Three of these followed cerebral haemorrhage. Some of the collected cases were of doubtful authenticity. More recently presumed cases of poliomyelitis were followed by widespread ossification of the soft tissues, involving the upper as well as the lower limbs (Drehmann, 1927; Costello and Brown, 1951; Freiberg, 1952). It is possible, however, that the illness, consisting of widespread and progressive muscle paralysis followed by ossification, was not due to the virus of poliomyelitis.

The aetiology of metastatic ossification is little understood. This is perhaps not surprising, considering that the exact biochemical mechanism of normal ossification has not yet been fully clarified (Best and Taylor, 1950). Almost all the writers quoted agreed that the biochemical studies of the serum were unhelpful, the figures for calcium, phosphorus and phosphatase being always normal. It is possible, however, that abnormalities might have been detected had estimations been carried out at a stage immediately preceding or at the beginning of the ossifications. Robison (1923) drew attention to the importance of phosphatase in the process of ossification. Wilkins, Regen and Carpenter (1935) found that in a case of progressive myositis ossificans biopsy specimens of muscles and fibrous tissue which were about to undergo ossification contained 800 to 1,600 times as much phosphatase as did normal muscle. They felt that this gross excess of phosphatase may lead to precipitation of calcium from normal serum, but it did not explain why normal cancellous bone should be formed and not amorphous calcification. Fibrous tissue within the muscles had the highest phosphatase content and this agreed with the histological observations of the

FIG. 1.—Case 1: extensive tuberculosis of left hip joint. Normal right hip joint. Diffuse bilateral soft tissue calcifications in adductors and flexors of both hip joints.

FIG. 2.—Case 1: right hip 10 months after admission. Ossification of adductors better defined.

FIG. 3.—Case 1: right hip 33 months after admission, following two operations for removal of ectopic bone. Dense scaffolding of new bone unites neck and head of the femur to the pelvis.

FIG. 4.—Case 3: right hip showing ill-defined ossification of iliopsoas tendon (six months after admission).
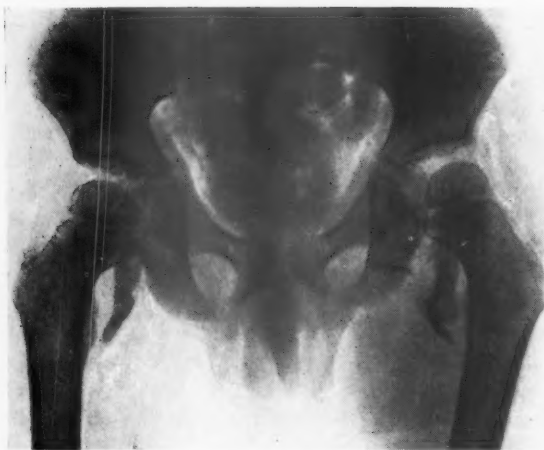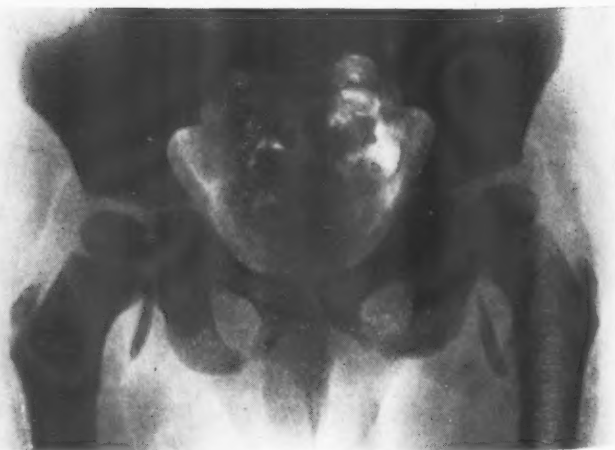
Fig. 5.—Case 3: six months later. Dense ossification of the right iliopsoas tendon.

Fig. 6.—Case 3: further 14 months later showing spontaneous partial absorption of the ectopic bone at its proximal half.

Fig. 7.—Case 4: bilateral ossifications of the iliopsoas tendons.

Fig. 8.—Case 4: ossifications both shorter and narrower one year later. Spontaneous absorption.

Fig. 9a and b.—Case 5: both hips showing considerable ossification of iliopsoas tendons three months after onset of paraplegia.
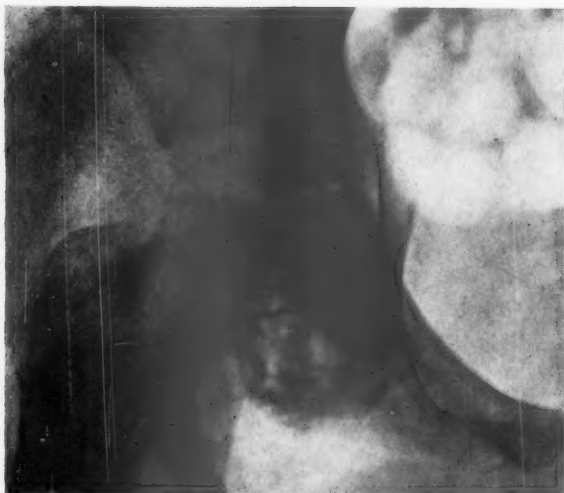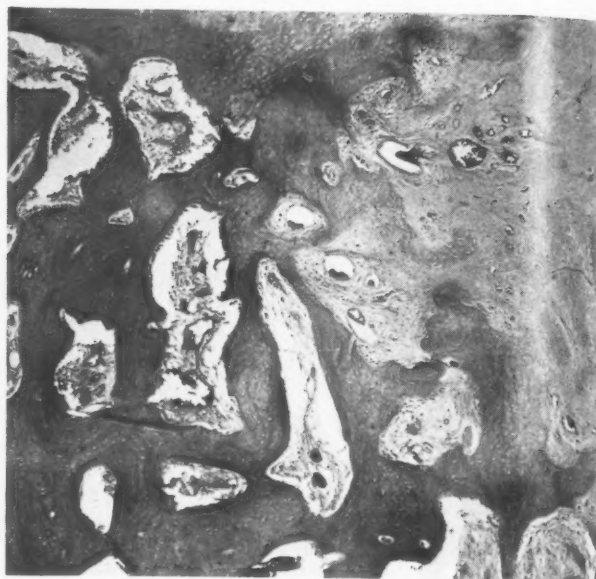
FIG. 10.

FIG. 12.
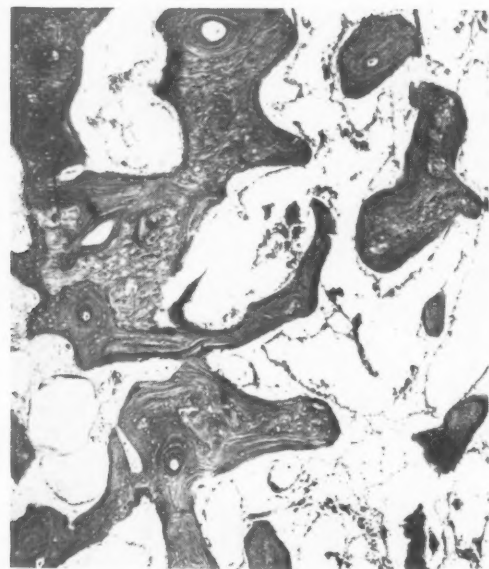
FIG. 13.

FIG. 11.

FIG. 10.—Case 5: right hip showing gross deposits of ectopic bone around the joint after a further period of three months

FIG. 11.—Case 5: necropsy specimen. Lateral view of right hip. Extreme degree of ectopic ossification in front of the joint.

FIG. 12.—Case 5: photomicrograph of the edge of the ossifying tendon. ×36.

FIG. 13.—Case 5: centre of the new bones, showing normal bone marrow. ×36.

previously quoted workers that fascial planes, ligaments and tendons ossify, not the muscle tissue itself. According to Watson Jones and Roberts (1934) fibroblasts or any mesenchymal cells may dedifferentiate and become capable of laying down bone. Other factors mentioned as necessary for pathological ossification are decreased oxygenation and blood supply (Leriche and Policard, 1926; Watson Jones and Roberts, 1934), local tissue damage (Vaughan, Sosman and Kinney, 1947) and decreased local CO_2 tension or increased alkalinity of the tissues (Wells, 1925).

Clinically, it seems that the factor necessary for the development of ectopic ossification is a spinal cord lesion with paraplegia in flexion, leading to muscle spasm and prolonged immobilization with consequent osteoporosis.

Summary

Ectopic ossification was demonstrated radiologically in five of 10 children who developed temporary paraplegia in flexion during streptomycin treatment of tuberculous meningitis and survived for more than three months. It was found two to six months after the onset of the paraplegia. In all cases the ossification affected the iliopsoas or the adductors of the thighs and their tendons below the level of the pelvis. The lesions were bilateral in three patients. They led to severe disability in two children by fixing the hip joints and to less severe symptoms in the others. Operative removal of the new bone in one child led to more extensive deposition of new bone and a worsening of his condition. In two conservatively treated patients there was subsequent radiological evidence of spontaneous absorption of new bone after recovery from meningitis.

The diagnosis was established radiologically in all patients and was confirmed at operation in one and at necropsy in another child. Histologically the ectopic tissue appeared to be normal bone with bone marrow.

The incidence and nature of neurogenic metastatic ossifications was reviewed. No previous instances in association with tuberculous meningitis have been found.

REFERENCES

Abramson, D. J. and Kamberg, S. (1949). *J. Bone Jt Surg.*, 31 A, 275.
Best, C. H. and Taylor, N. B. (1950). *The Physiological Basis of Medical Practice*, 5th ed., pp. 827-830. London.
Costello, F. V. and Brown, A. (1951). *J. Bone Jt Surg.*, 33 B, 594.
Dejerine, Mme., Ceillier, A. and Dejerine, Y. (1919). *Rev. Neurol., Paris*, 26, 399.
Drehmann, G. (1927). Abstracted *Zbl. ges. Neurol. Psychiat.* (1928), 48, 686.
Freiberg, J. A. (1952). *J. Bone Jt Surg.*, 34 A, 339.
Geldmacher, M. (1925). *Dtsch. Z. Chir.*, 191, 180.
Hanke, H. (1943). *Ibid.*, 258, 217.
Heilbrun, N. and Kuhn, W. G., Jr. (1947). *Radiology*, 48, 579.
Leriche, R. and Policard, A. (1926). *Les problèmes de la physiologie normale et pathologique de l'os.* Paris.
Lüdeke, H. (1950). *Fortschr. Röntgenstr.*, 73, 564.
Miller, L. F. and O'Neill, C. J. (1949). *J. Bone Jt Surg.*, 31 A, 283.
Robison, R. (1923). *Biochem. J.*, 17, 286.
Soule, A. B., Jr. (1945). *J. Neurosurg.*, 2, 485.
—— and Stiff, D. W. S. (1949). *Bull. U.S. Army med. Dep.*, 9, 1018.
Stanger, J. K. (1947). *J. Bone Jt Surg.*, 29, 107.
Vaughan, J. H., Sosman, M. C. and Kinney, T. D. (1947). *Amer. J. Roentgenol.*, 58, 33.
Voss, H. (1937). *Fortschr. Röntgenstr.*, 55, 423.
Watson-Jones, R. and Roberts, R. E. (1934). *Brit. J. Surg.*, 21, 461.
Wells, H. G. (1925). *Chemical Pathology*, 5th ed., p. 486. Philadelphia.
Wilkins, W. E., Regen, E. M. and Carpenter, G. K. (1935). *Amer. J. Dis. Child.*, 49, 1219.

IDIOPATHIC HYPOPROTEINAEMIC OEDEMA AND AMINO-ACIDURIA IN AN INFANT

BY

J. P. BOUND and W. R. HACKETT

From the Departments of Paediatrics and Biochemistry, Hillingdon Hospital, Middlesex

Hypoproteinaemic oedema may result from a deficiency of protein in the diet or interference with its absorption from impaired synthesis of serum proteins in the liver, or from loss of protein, as in albuminuria. In some cases, termed idiopathic hypoproteinaemia, the cause is obscure. A few examples in children are on record. Schick and Greenbaum (1945) described an 11-year-old girl who had had recurrent oedema from birth: the serum albumin and globulin, and especially γ globulin, were decreased. In the case of a boy reported by Hertzog and Faust (1950) the serum proteins had returned to normal when he was 5 months old.

Homburger and Petermann (1949) described a syndrome of idiopathic familial dysproteinaemia characterized by abnormalities in the electrophoretic patterns of the plasma with or without hypoprotein- aemia. These were accompanied in the adult by peripheral vascular changes and oedema. In no case was the albumin lowered to the extent usually re- quired to produce oedema, and a constitutional inferiority of the vascular system was postulated. Although oedema did not appear until after puberty, it is of interest that the mother of certain of the cases had five oedematous, stillborn foetuses although she was Rh positive.

Disorders of amino-acid metabolism have been reviewed by Dent (1951). Apart from easily dis- tinguished abnormalities in which a specific amino- acid is excreted in the urine (e.g. phenylpyruvic oligophrenia), there is a group of conditions in which cystine, with or without various other amino-acids, is found in increased amounts in the urine. This group Dent divided into (1) renal cystinuria, where there is a normal concentration of cystine in the plasma and amino-aciduria results from a lowered renal threshold, and (2) hepatic cystinuria, in which amino-aciduria is a reflection of a raised plasma concentration of cystine and other amino-acids. Renal cystinuria includes the de Toni-Debré-Fanconi

syndrome, Wilson's disease and the condition long known as cystinuria, in which renal calculi made of cystine may be formed. Hepatic cystinuria occurs in mild and chronic disorders of the liver, as well as in more severe affections such as acute yellow atrophy.

More recently, Holzel, Komrower and Wilson (1952) have reported the occurrence of amino- aciduria in two cases of galactosaemia. In this con- dition hepatic damage may occur, and Mellinkoff, Roth and MacLaggan (1945) reported the case of a boy who developed oedema, associated with lower- ing of the plasma proteins and hepatomegaly, at the age of 6 weeks.

It will be seen that, among the causes of hypo- proteinaemic oedema and amino-aciduria respective- ly, hepatic disease and galactosaemia are common to both. Although hepatomegaly may be a feature of the de Toni-Debré-Fanconi syndrome, alteration of the serum proteins is not found (Debré, 1947). In the family with idiopathic dysproteinaemia described by Homburger and Petermann (1949) the amino-acids of the plasma and urine were studied by chromato- graphy and no abnormalities found. Thus, in an infant showing both hypoproteinaemic oedema and amino-aciduria, other evidence of liver disease or of galactosaemia might be expected. In the case to be presented no such evidence was found.

Case Report

D.B., a boy aged 1 month, was admitted to Hillingdon Hospital on September 13, 1950. He was the fourth child, and had been born at home by a forceps delivery, the birth weight being 10 lb. Swelling of the feet was noticed at birth, and four days before admission the legs had also become swollen. He had been entirely breast fed, but the mother thought that she had insufficient milk, and he had gained only 4 oz. over his birth weight. There had been no diarrhoea or vomiting.

The first sibling, a girl, had swelling of the feet from birth, and had pitting oedema of the feet and legs when
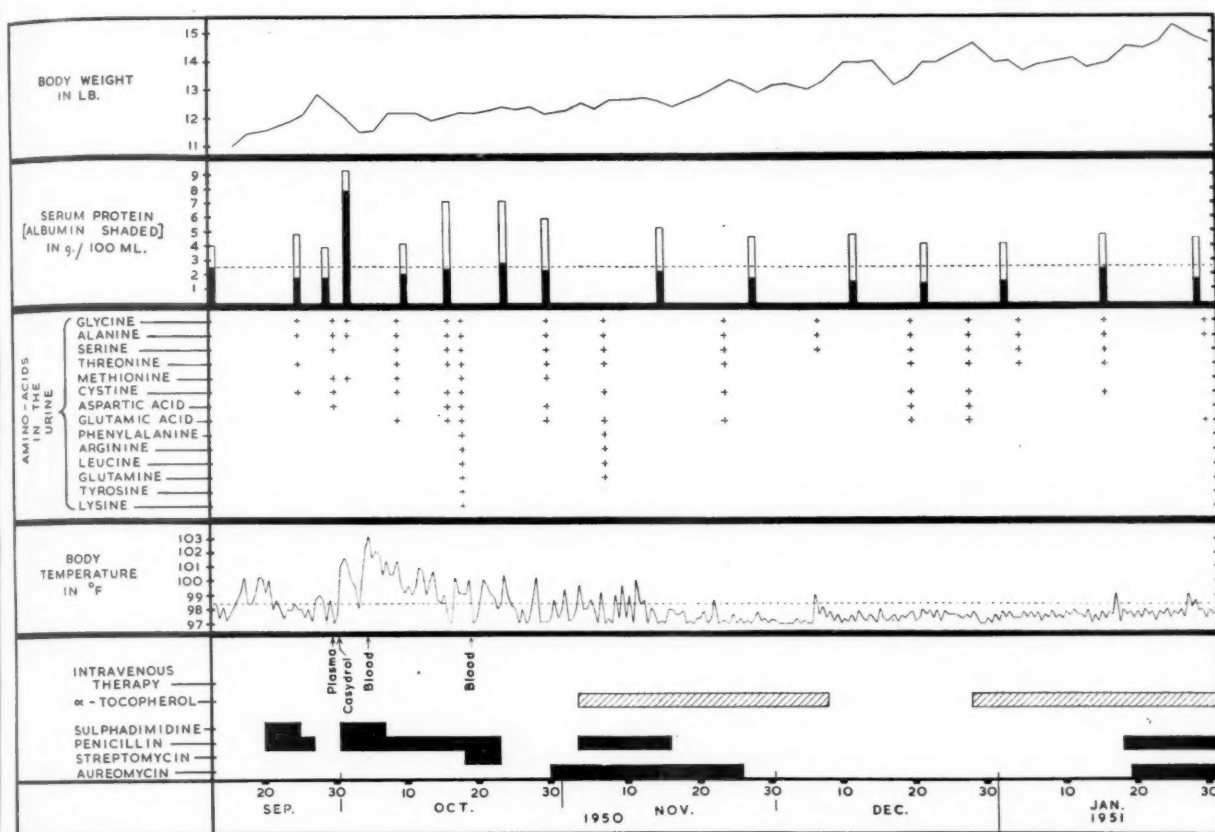
FIG. 1.—Chart of progress and treatment during the first four-and-a-half months.

seen at another hospital at the age of 7 weeks. Subsequently oedema of the trunk and arms was noted, and ascites gradually developed, paracentesis being performed on several occasions. She died at the age of 6 months, and during the previous week two estimations of the total serum proteins gave values of 3·05 and 3·4 g./100 ml. respectively. At necropsy, in addition to the oedema and ascites, osteomyelitis of the fourth and fifth right ribs and the manubrium sterni, a purulent pericarditis and multiple staphylococcal abscesses of the lungs and kidneys were demonstrated. The liver was macroscopically normal, but frozen sections showed extensive fatty infiltration, with a degree of portal cellular reaction. There was no obstruction of the superior or inferior vena cava or of the thoracic duct.

Two other children, a girl aged 3 years and a boy aged 1 year and 10 months, were alive and well. The parents were not related. The two healthy children and the parents had normal serum proteins as demonstrated by electrophoresis and chemical analysis, and no increased urinary excretion of amino-acids.

On examination marked pitting oedema of the feet and legs, and a lesser degree of oedema of the thighs, sacrum, hands and forearms was seen. There was no clinical anaemia. The heart was not enlarged, and no murmurs

were audible. The baby had a nasal discharge but the lungs were clear, apart from rhonchi at the right base. The abdomen was slightly protuberant and showed a small umbilical hernia: the liver and spleen were not palpable. There was no neck rigidity.

The main features of the boy's progress during the first four and a half months are shown in Fig. 1.

Laboratory Investigations. During the first two weeks after admission the following investigations were carried out.

The urine showed no albumin or reducing substance, and the centrifuged deposit yielded a few leucocytes only.

A radiograph of the chest revealed no pulmonary lesion, and the cardiac contours were normal.

A blood count gave haemoglobin 13 g. per 100 ml.; red cells 3·84 million per c.mm.; leucocytes 11,500 per c.mm. (53% neutrophils, 40% lymphocytes and 7% monocytes). The sedimentation rate was 17 mm. in one hour (Westergren).

The total serum protein was 4·0 g. per 100 ml. (albumin 2·5 g. per 100 ml., globulin 1·5 g. per 100 ml.). (Globulin precipitation was carried out by the method of Cohn and Wolfson, 1948.)

The serum bilirubin level was less than 0·2 mg. per 100 ml. The alkaline phosphatase was 14 King-Armstrong

units per 100 ml. Thymol turbidity was 0 units. Kunkel's specific gamma globulin test (zinc sulphate turbidity) gave 0 units. The serum inorganic phosphorus level was $6 \cdot 3$ mg. per 100 ml.; serum chloride level 632 mg. per 100 ml. (as sodium chloride); blood cholesterol level 130 mg. per 100 ml.; blood urea 30 mg. per 100 ml.; blood galactose 0 mg. per 100 ml. The blood Wassermann reaction was negative.

Urine chromatography showed heavier bands of glycine and alanine than in the urine of a normal baby, and in addition, threonine and a trace of cystine were present (Fig. 2a). For all chromatographs 25 microlitres of an early morning specimen of urine were used, and run in phenol-water.

having fallen to 8 g. per 100 ml. and the red cells to $2 \cdot 5$ million per c.mm., a transfusion of 120 ml. of packed red cells was given.

Eleven days later two abscesses were noted along the line of the cephalic vein above the site of the previously septic wound. Pus was aspirated, and culture produced coliform organisms and coagulase-positive penicillin-resistant staphylococci. A five-day course of strepto-mycin was given in addition to the penicillin but this did not influence the pyrexia, and both drugs were stopped. At this time a further transfusion of 200 ml. of blood was given for anaemia (haemoglobin $8 \cdot 6$ g. per 100 ml.).

On October 29 purulent arthritis of the right knee developed, and led to the discovery of an area of osteomye-

FIG. 2.—One-dimensional chromatograms.

During this period the oedema increased with the development of gross swelling of the lower legs and scrotum, ascites and puffiness of the eyelids. On September 17 pyrexia developed, for which no cause was found. A course of penicillin and sulphadimidine was begun on the fourth day, and the pyrexia rapidly subsided. The infant was fed on half cream National dried milk, and received daily supplements of vitamins A, D and C. Vitamin B complex was given intramuscularly daily for five days, and thereafter weekly.

Period of Increasing Amino-Aciduria. On September 29 1 pint of plasma was given intravenously, and resulted in a profuse diuresis and marked diminution in the oedema. The plasma was followed by injection of intra-venous 'casydrol', which caused some increase in the amino-aciduria. Two days after the administration of plasma pyrexia appeared again, and the intravenous drip wound was noted to be inflamed. Penicillin was admin-istered, together with sulphadimidine for the first six days, but some fever persisted. On October 4, the haemoglobin

litis in the upper part of the right femur and a small focus in the left tibia. Aureomycin therapy was begun, and subsequently penicillin was restarted in a larger dose than previously.

Throughout this five-week period a variable degree of oedema of the feet and legs persisted. A striking feature was the increasing amino-aciduria shown by the one-dimensional chromatograms (Fig. 2b). On October 19, when seven bands were identified as on October 17, a two-dimensional chromatogram revealed 15 amino-acids and one unidentified substance. These findings were confirmed for us by Dr. C. E. Dent of University College Hospital (Fig. 3). At this time the serum amino nitrogen level, estimated by the method of Albanese and Irby (1945), was $8 \cdot 6$ mg. per 100 ml.

Period of Therapy with Vitamin E. On November 3 oral administration of α-tocopherol, 150 mg. daily, was begun. Six days later swelling of the right shoulder was found to be due to osteomyelitis of the upper end of the humerus. On November 15 a radiograph of the femora

showed that there was osteo-myelitis of the upper end of the bone on the left side, as well as on the right. By November 26 the temperature had been nor-mal for two weeks, the swellings caused by the osteomyelitis were subsiding, and the sedimentation rate was only 9 mm. in the first hour: aureomycin was with-drawn, and no evidence of a relapse followed. Amino-acid-uria had reached its maximum on November 7 (Fig. 2c) and there-after decreased, being almost normal on December 7 (Fig. 2d). There was some increase in the oedema of the feet and legs.

On December 8 therapy with α-tocopherol was stopped for three weeks. During this period the infant's feeds were gradually changed to full cream National dried milk, and on December 16 'casilan' was added to them. The amino-aciduria increased again, and on December 28 approached the previous maxi-mum (Fig. 2e). The increased oedema persisted. There was no clinical evidence of any active infection, and radiographs (December 20) showed very marked reconsolidation of the areas of osteomyelitis.

I. Cystine, 2."W"-spot, 3. Glutamic acid, 4. Serine,
5. Glycine, 6. Threonine, 7. Alanine, 8. Glutamine, 9. Tyrosine,
10. Phenylalanine, 11. Leucine, 12. Valine, 13. Histidine,
14. β-amino-isobutyric acid, 15. Lysine, 16. Arginine.

FIG. 3.—Two-dimensional chromatogram of October 19, 1950.

On December 28 a second course of therapy with α-tocopherol was begun, and continued for 30 weeks. After one week the amino-aciduria again showed a marked reduction (Fig. 2f) and oedema decreased. On January 15, 1951, a recurrence of the osteomyelitis of the left tibia, with subperiosteal abscess formation but little pyrexial response, was associated with a mild, temporary increase in amino-aciduria, the serum amino nitrogen level being 6·4 mg. per 100 ml. The infection subsided with a further course of aureomycin and penicillin. On February 24 the infant developed bronchitis with initial diarrhoea. There was a considerable increase in amino-aciduria (Fig. 2g), with a serum amino nitrogen level of 9·1 mg. per 100 ml. When this infection was controlled amino-acid excretion soon diminished and was subse-quently either normal or slightly increased. The serum amino nitrogen level was then 5·3 mg. per 100 ml. Oedema increased temporarily with each infection, but thereafter was minimal.

During the first four and a half months of this second course of α-tocopherol, the total serum protein concen-tration lay between 3·35 and 5·35 g. per 100 ml. and the albumin between 1·35 and 2·4 g. per 100 ml. with an albumin-globulin ratio of 0·5 to 1·2. On May 11 1 pint of plasma was given intravenously and produced a diuresis. The total serum protein concentration was not altered, but the serum albumin persisted above 2 g. per 100 ml. and the albumin-globulin ratio was normal for three weeks. Subsequently, the serum albumin concen-tration was again less than 2 g. per 100 ml. on occasions, with an albumin-globulin ratio down to 0·6. Fractiona-tion of the serum proteins according to the method of Martin, Morris and Smith (1950) on May 31 showed albumin 2·76 g. per 100 ml., α globulin 0·87, β globulin 0·37 and γ globulin 0·10 g. per 100 ml.

At the end of February, when the infant was 6 months old, cereal was added to his feeds, and over the next three months a weaner's diet was gradually introduced, still with the addition of 'casilan'. On June 4 he was dis-charged home, and kept under observation in the Out-patient Department. α-Tocopherol was stopped on July 23.

Follow-up Period. Over the next 10 months he re-mained well, apart from a persistent nasal discharge at first. Minimal oedema of the feet was sometimes present, but often there was none. Amino-acid excretion in the urine was normal or slightly raised. On December 21, 1951, liver function tests showed the serum bilirubin to be less than 0·2 mg. per 100 ml., the alkaline phosphatase 17 King-Armstrong units per 100 ml., thymol turbidity 1 unit and total serum proteins 5·7 g. per 100 ml. (al-bumin 2·3, α globulin 3·0, β globulin 0·4 and γ globulin 0 g. per 100 ml.).

On May 15, 1952 (at the age of 21 months), his general development was satisfactory, except that he had not walked until the age of 19 months, and had a waddling gait. A radiograph revealed subluxation of the right hip. There was minimal oedema of the feet. The total serum protein was 3·55 g. per 100 ml. (albumin 2·05 and globulin 1·50 g. per 100 ml.). Serum electrophoresis showed that most of the globulin was β globulin with rather less α 2 globulin: there was a trace of α1 globulin and γ globulin was absent (Fig. 4). The serum amino nitrogen level was 6·6 mg. per 100 ml. Urine chromatography showed normal amounts of glycine and alanine, with a trace of cystine, aspartic acid, serine and threonine (Fig. 2h). The Schick test was negative.

and galactosuria was absent. Further, when amino-aciduria was marked the pattern of the two-dimensional chromatogram, with cystine and lysine predominating, was unlike that of hepatic disease, although the W-spot had previously been seen only in such cases (Dent, 1950). Finally, hypoprotein-aemia in hepatic disease is almost entirely due to a lowered concentration of serum albumin, whereas an additional feature in our case was the virtual absence of γ globulin.

At this point it must be remembered that the first sibling had also shown oedema from birth, and had a

FIG. 4.—Electrophoresis of serum proteins on May 15, 1952.

Discussion

Initial investigation in our case showed that the oedema was related to hypoproteinaemia. The boy was not premature, and there was no evidence of anaemia or of cardiac or renal disease. When the serum albumin fell below 2 g. per 100 ml. the oedema tended to increase rapidly, and when the albumin level was raised by plasma transfusion a marked diuresis occurred. The hypoproteinaemia was not due to a lack of pro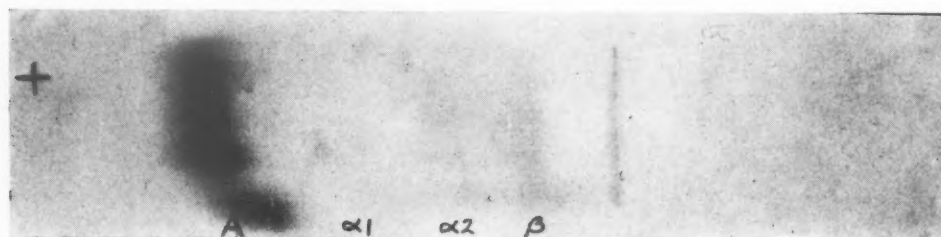tein in the diet or to an absorption defect, as symptoms were present from birth. Albuminuria was consistently absent. It appeared, therefore, that synthesis of the serum proteins was impaired.

On two occasions when amino-aciduria was marked, the serum amino nitrogen level was much higher than at other times, This suggested that the increased amino-aciduria reflected the raised serum level of amino-acids as in Dent's group of hepatic cystinuria. It has already been shown how the combination of hypoproteinaemic oedema and amino-aciduria might be expected to result from liver disease and so far the facts in our case appeared to fit in with this concept. Thompson, McQuarrie and Bell (1936) described a child in whom hypo-proteinaemia was thought to result from an atrophy of hepatic cells and this was demonstrated at necropsy.

In our case no confirmatory evidence of hepatic disease was found: icterus and hepatomegaly were never present, other liver function tests were normal

deficiency of the total serum proteins for which no cause was found. At necropsy the liver was macro-scopically normal and the fatty infiltration probably resulted from the widespread staphylococcal infection. It seems likely that the symptoms of the two siblings were due to the same cause, and we suggest that they suffered from an inherent abnormality of amino-acid metabolism, manifested chiefly by an idiopathic hypoproteinaemia. The occurrence of intermittent amino-aciduria does not appear to have been noted previously in this condition.

Himsworth and Lindan (1949) discussed experimental work which showed that supplements of α-tocopherol reduced the liability of rats to develop massive hepatic necrosis due to cystine deficiency. We felt that the possibility that tocopherol was concerned in amino-acid metabolism warranted its trial in our case. During the first course of treatment a marked decrease in the amino-aciduria occurred. But the original increase in amino-aciduria was synchronous with infection, and this was being controlled with antibiotics during treatment with toco-pherol. Therefore the improvement could have been due to control of infection alone. When tocopherol was withdrawn the amino-aciduria again increased, although at this time there was no evidence of any active infection. A second course of tocopherol was associated with a rapid improvement. Subsequently, amino-aciduria was normal or slightly in excess, but it increased temporarily on two occasions with inter-current infections while tocopherol was still being

administered. When tocopherol was finally withdrawn no increase in amino-aciduria resulted. Thus, there was little evidence of any beneficial effect from tocopherol. The most that could be said was that the effect of the initial withdrawal, and the early effect of the second course, suggested that improvement in amino-aciduria was hastened by the vitamin at that time.

The relationship of increased amino-aciduria to infections was presumably due to the accompanying increase in protein catabolism which would enhance the effects of any already existing abnormality. The serum proteins were abnormal throughout. Although their total value was occasionally normal, the albumin was always low, only rarely exceeding a value of 2·5 g. per 100 ml., below which oedema tends to occur, and γ globulin was virtually absent.

Schick and Greenbaum (1945) expressed surprise that their case of congenital hypoproteinaemia showed no susceptibility to infections in view of the absence of γ globulin, which is accepted to be the main carrier of humoral antibodies. However a negative Schick test demonstrated the presence of a certain amount of these antibodies. Our case also had a negative Schick test, but it is of interest that both siblings developed widespread staphylococcal infections. Inability to form γ globulin appears to increase susceptibility to a certain type of infection at least.

Summary

An infant who had hypoproteinaemic oedema from birth is described. The serum albumin concentration was persistently low, and γ globulin virtually absent. The presence of intermittent amino-aciduria is emphasized.

There was a history of a sibling with hypoproteinaemic oedema for which no cause was found.

It is postulated that both infants suffered from an inherent abnormality of amino-acid metabolism manifested chiefly as idiopathic hypoproteinaemia.

Both developed widespread staphylococcal infections.

α-Tocopherol had very little, if any, effect on the progress of the present case.

REFERENCES

Albanese, A. A. and Irby, V. (1945). *J. Lab. clin. Med.*, **30**, 718.
Cohn, C. and Wolfson, W. Q. (1948). *Ibid.*, **33**, 367.
Debré, R. (1947). *Le Syndrome de Diabète Rénal*, p. 30. Paris.
Dent, C. E. (1950). Personal Communication.
—— (1951). *Expos. ann. Biochim. méd.*, **13**, 79.
Hertzog, F. V. and Faust, O. A. (1950). *J. Pediat.*, **36**, 641.
Himsworth, H. P. and Lindan, O. (1949). *Nature, Lond.*, **163**, 30.
Holzel, A., Komrower, G. M. and Wilson, V. K. (1952). *Brit. med. J.*, **1**, 194.
Homburger, F. and Petermann, M. L. (1949). *Blood*, **4**, 1085.
Martin, N. H., Morris, R. and Smith, M. (1950). *J. clin. Path.*, **3**, 266.
Mellinkoff, S., Roth, B. and MacLaggan, J. (1945). *J. Pediat.*, **27**, 338.
Schick, B. and Greenbaum, J. W. (1945). *Ibid.*, **27**, 241.
Thompson, W. H., McQuarrie, I. and Bell, E. T. (1936). *Ibid.*, **9**, 604.

FATAL GENERALIZED VACCINIA WITH FAILURE OF ANTIBODY PRODUCTION AND ABSENCE OF SERUM GAMMA GLOBULIN

BY

S. E. KEIDAN, K. McCARTHY and J. C. HAWORTH

From the Departments of Bacteriology and Child Health of the University of Liverpool and Alder Hey Children's Hospital

The reaction to vaccination against smallpox is generally a trivial, short-lived affair. Complications are uncommon and, of these, generalized vaccinia is one of the least common. In true generalized vaccinia the lesions pass through the stages of papule, vesicle and pustule with little cropping, and the first lesions seldom occur earlier than the ninth day after vaccination. In most cases the disease is self-limiting, the lesions heal normally, and neutralizing antibodies develop during the course of the disease. A small number of cases have been reported, however, in which lesions continued to develop over a period of weeks or months. Nearly all of these have been fatal. A further case of this type is reported here.

Case Report

E.H., a girl, was born by normal delivery at full term on September 24, 1951, and weighed 6 lb. 5 oz. at birth. The parents, who were first cousins, were quite healthy. The mother had been unsuccessfully vaccinated in infancy and had not been re-vaccinated. The father had been successfully vaccinated in infancy and re-vaccinated in 1944. This resulted in a normal reaction. The only sibling had died at the age of 5 months from bronchopneumonia and had not been vaccinated. The baby had been breast fed for four weeks and was then weaned on to 'lacidac'; supplements of cod liver oil and ascorbic acid had been given, and up to the time of vaccination she had been very well and gaining weight normally.

E.H. was vaccinated on the left deltoid region on November 22, 1951, at the age of 8 weeks. A small vesicle was visible on the vaccination site one week later and two weeks after vaccination further vesicles were observed around the primary lesion. Several others were noticed around the vulva and anus about the same time. Seventeen days after vaccination a small vesicle developed on the dorsum of the left hand. The child had mild diarrhoea following the vaccination but had taken her feeds well and had not been vomiting.

She was admitted to Alder Hey Children's Hospital on December 13 at the age of 11 weeks. Examination showed a healthy-looking infant with a good colour, weighing 8 lb. 8½ oz. The rectal temperature was 99° F. At the vaccination site on the left deltoid region was a yellowish ulcerated area 2·5 cm. in diameter surrounded by numerous vesicles, varying in size from 5 to 20 mm. in diameter, and containing clear fluid (Fig. 1). A number of large umbilicated vesicles surrounded the vulva and

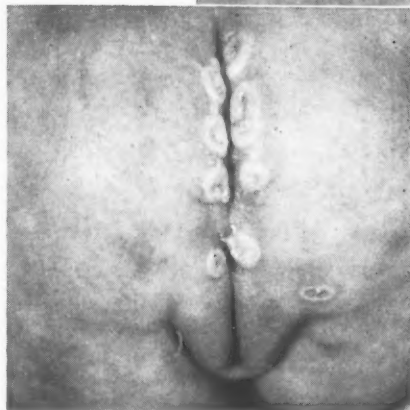FIG. 1.—Primary and secondary lesions three weeks after vaccination.

FIG. 2.—Secondary vesicles around anus and vulva three weeks after vaccination.

110

anus (Fig. 2). Other single vesicles were on the upper lip, the right side of the face, the dorsum of the right hand (Fig. 3), the right leg, the left heel, and there were a few lesions on the back. No lesions were seen in the mouth. Neither the spleen nor any lymph nodes were palpable. A provisional diagnosis of generalized vaccinia was made.

FIG. 3.—Lesions on the face and the right hand three weeks after vaccination.

From the time of her admission until her death four weeks later there was steady deterioration in her condition. The vesicles on the left deltoid area coalesced and eventually formed a large ulcer with a granulating base and rolled vesicular edge (Fig. 4). Vesicles continued to appear on the face, scalp and the rest of the body in a centrifugal distribution. Many of the lesions coalesced and, like the primary lesion, formed large, spreading

FIG. 4.—Primary lesion five weeks after vaccination. Secondary lesions at various stages of development can be seen on the scapular region and the arm.

ulcers. Lesions in the nostrils led to nasal obstruction and interfered with feeding. The eyelids became involved two weeks before death but the eyes themselves were not affected (Fig. 5). In the mouth ulcers appeared on the tongue, the palate and the cheeks. The cry became hoarse and laryngeal involvement was suspected. None of the lesions ever showed any signs of healing and there was little evidence of inflammatory reaction except for an area of cellulitis surrounding deep ulcers on the left foot The spleen and lymph nodes were never enlarged. There

FIG. 5.—Spreading lesions on the face six weeks after vaccination.

was little fever, the rectal temperature rarely exceeding 100° F. Feeds were taken poorly and she developed diarrhoea during the last fortnight. She steadily lost weight and was only 6 lb. 9 oz. shortly before death.

Investigations. Blood culture on December 24 showed a profuse growth of *Staphylococcus aureus* (coagulase positive) and enterococci. The staphylococcus was sensitive to chloromycetin and aureomycin and slightly sensitive to penicillin. On January 2 *Staphylococcus aureus* (coagulase positive) was cultured.

The Wassermann reaction was negative.

A swab from infected skin lesions taken on December 27 gave a profuse growth of *Staphylococcus aureus* (coagulase positive).

On January 1, 1952, following transfusion, a full blood count gave: haemoglobin, 96%; leucocytes 6,700 per c.mm. (corrected) (myelocytes, 871 or 13%, band cells, 871 or 13%, polymorphs, 4,221 or 63%, lymphocytes, 134 or 2%, monocytes, 603 or 9%). Normoblasts were 55 per 100 leucocytes. The red blood cells showed anisocytosis, polychromasia and punctate basophilia.

On January 3 the leucocytes were 6,000 per c.mm. (metamyelocytes, 540 or 9%, myelocytes, 60 or 1%, band cells 3,840 or 64%, polymorphs, 1,200 or 20%, lymphocytes, 120 or 2%, monocytes, 240 or 4%).

Treatment. From the time of her admission penicillin, 250,000 units and later 125,000 units, was given six-hourly intramuscularly. Aureomycin, 100 mg. six-hourly by mouth, was given from December 27 until the time of death. Local treatment consisted of the application of penicillin powder and tulle gras to the skin lesions and 1% gentian violet to the mouth. On December 22 60 ml. of serum from a recently vaccinated donor (A) was given intravenously. On December 31, 250 ml. of whole blood from another recently vaccinated donor (M) was transfused after removal of 100 ml. of the child's blood to prevent circulatory overloading. On January 4, 500 mg. of gamma globulin was given intramuscularly and a further 250 mg. the following day.

She died on January 6, 1952, seven weeks after vaccination.

Post-mortem Report. Post-mortem examination was made 18 hours after death by Dr. E. G. Hall. Inspection showed the wasted body of a female infant. Scattered over the skin of the whole body, but especially marked on the extremities and face, were numerous lesions ranging from minute vesicles to crusted ulcers. Lymph nodes throughout the body were of approximately normal size and did not show any macroscopic abnormality. Scanty minute petechiae were present on the visceral pericardium and the right auricle was dilated but otherwise the cardiovascular system was normal. There were ulcers on the tip and lateral borders of the tongue and a few on the soft palate. The laryngeal orifice was narrowed by oedema of the aryepiglottic folds spreading from an ulcer 5 mm. in diameter, lying on the anterior surface of the laryngo-pharynx and immediately behind the arytenoid cartilage. In the lungs there was bilateral bronchopneumonic consolidation involving the lower lobes and portions of the upper and middle lobes. The liver was rather pale but otherwise normal. The spleen was small, firm and of normal colour. The right adrenal was completely destroyed by haemorrhage which extended into the extra-peritoneal tissues on that side, and there was a small haematoma, 5 mm. in diameter, in the antero-medial aspect of the left adrenal. The brain showed slight congestion but was otherwise normal.

Histology. All tissues were fixed in formol Zenker for six hours and sections stained by haematoxylin and eosin and also by eosin and methyl blue.

A small piece of skin from the scalp, only 2 cm. long, showed on section lesions in several stages of development ranging from an early focus, involving only a few cells, to a late lesion, beginning to crust. A typical early vesicle about 4 mm. in diameter was present on the sole of the foot. Microscopic examination showed a vesicle situated fairly deeply in the epidermis. Inclusion material was present in large amounts in the surviving epithelial cells of the vesicle floor between the papillae of the corium. Many of these basal cells were full of strongly acidophilic cytoplasmic inclusion material with only a ghost of a degenerate nucleus discernible. One striking feature was an almost complete lack of infiltration by inflammatory cells (Fig. 6). These two features, lack of inflammatory response and large amounts of coarsely granular inclusion material, characterized all the skin lesions examined. One of the scalp lesions contained what appeared to be pus, but on examination this was found to be composed of epithelial debris with very few polymorphs. The lung showed congestion and oedema of the alveolar walls with very few inflammatory cells. The liver, kidney, brain and a salivary gland were also

sectioned but showed no abnormality. A section of an axillary lymph node showed large numbers of monocytes and plasma cells. Germinal centres and lymphocytes were completely absent (Fig. 7). The spleen showed very few Malpighian corpuscles and those which were present were made up mainly of plasma cells and monocytes. No lymphocytes or lymphatic tissue were seen.

Virus Studies. On December 13, the day of admission to hospital, scrapings were taken from the base of a typical secondary vesicle. Smears made from these were fixed and stained by Gutstein's method using alkaline methyl violet. Large numbers of elementary bodies were present, indistinguishable from those seen in smears from cases of smallpox. Swabs were taken from a typical early

FIG. 6.—Section of vesicle from sole of foot showing absence of inflammatory cells in the dermis (low power haematoxylin and eosin).

lesion on the face and from the base of one of the peri-anal ulcers. After treatment with antibiotics extracts in varying dilutions were inoculated on to the chorio-allantoic membrane of 12-day chick embryos. Blood, obtained from the baby by jugular puncture on December 13, was divided into two parts, one of which was hepar-inized and the other allowed to clot. The heparinized whole blood was lysed by alternate rapid freezing and

FIG. 7.—Section of axillary lymph node showing absence of germinal centres.

thawing in alcohol-solid CO_2 and 0·4 ml. was then inoculated on to the chorio-allantois of each of four eggs. The serum was separated from the clotted blood and stored at −78° C.

After three days' incubation the eggs inoculated with the swab extract showed typical isolated vaccinial lesions from the higher dilution while the lower dilution showed confluent lesions. Microscopical examination of sections of confluent lesions showed proliferation of the ecto-dermal cells, which contained large amounts of acido-philic intra-cytoplasmic granular inclusion material when stained with eosin and methyl blue.

The pock counts in the four eggs inoculated each with 0·4 ml. of whole blood ranged from 20 to 30 so that more than 50 infective particles per ml. must have been present in the child's blood at this time. The site of the vene-puncture was free from visible skin lesions, nor did a skin

lesion subsequently develop where the needle pierced the skin.

In addition to this first blood sample taken three weeks after vaccination, further samples of heparinized and clotted blood were obtained as follows:

18.12.51. Thirty infective particles (vaccinia virus) per ml. were recovered from this heparinized blood sample.

23.12.51 (four weeks after vaccination). Five infective particles per ml. were recovered. (This sample was taken 18 hours after administering 60 ml. of serum from a well vaccinated donor (A) whose serum was known to contain neutralizing antibody.)

31.12.51 (five and a half weeks after vaccination). One hundred and ten infective particles per ml. were recovered. However, by this time cutaneous lesions were fairly wide-spread, and although there were no visible lesions at the site of the puncture, the skin may have become contamin-ated with virus from neighbouring lesions. Nevertheless, a viraemia was almost certainly present at this time, for skin lesions continued to appear up to the time of death one week later.

A further transfusion given on December 31 consisted of 250 ml. of homologous citrated whole blood taken three hours previously from a different donor (M). It was known from previous investigations of the sera of these two donors that there would be less antibody in serum (M) but it was thought that whole blood might be more effective, and this donor was of the same blood group as the baby.

7.1.52. The last sample of blood from the baby was obtained 18 hours after death. This was one week after administering the whole blood and two days after giving the gamma globulin. This sample was obtained after the body had been opened and skin contamination of the blood samples can be ruled out. Approximately 100 infective particles per ml. were found.

A number of organs removed at necropsy were also examined for virus, precautions having been taken against accidental contamination from the skin. Fragments were ground up, cultured on blood agar, and extracted with M-250 phosphate buffer pH 7·2 containing 100 units per ml. of penicillin and streptomycin. The extracts were then inoculated on to the chorio-allantoic membrane of chick embryos. Unfortunately most of the organs (lung, liver, spleen, kidney, brain) were so heavily contaminated with *Bact. coli* that the embryos died. Surprisingly, however, the extract of an axillary lymph node and of the bone marrow were bacteriologically sterile, and on egg culture the bone marrow extract yielded 100 lesions per egg (i.e. approximately 1,000 infective particles per gramme of mar-row) and the lymph node extract produced semi-confluent lesions (corresponding to 10,000 particles per gramme).

Vaccinia virus was also recovered at necropsy from the skin lesions.

The cerebrospinal fluid was sterile on bacteriological culture and no virus was recovered from it.

The serum samples obtained from the baby on various dates were stored at −78° C. and later tested for virus neutralizing antibodies. Mixtures of the various samples of serum and a known fixed quantity of virus were inocu-lated on to the chorio-allantoic membranes of groups of
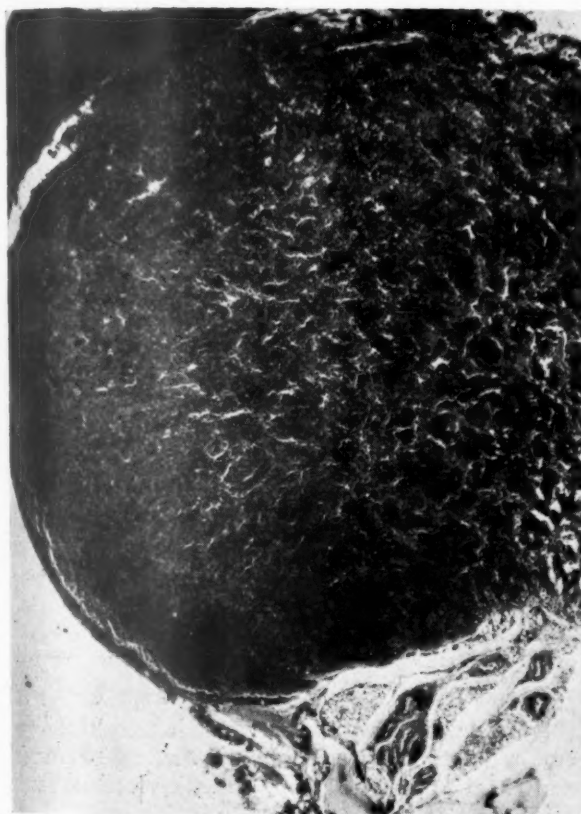
six 12-day-old chick embryos. The reduction in the number of pocks resulting from the inoculation of virus-serum mixtures made with immune sera compared with those made with normal serum from an unvaccinated subject was used as a measure of the antibody content of the sera under test. For these tests smallpox virus was used. It was desirable not to use vaccinia virus in these tests since some of the serum samples to be tested already contained vaccinia virus (see above).

The method of testing for serum antibody has been published elsewhere (McCarthy and Downie, 1948). In addition the samples were also tested unheated after storage at −78° C.

The samples tested were obtained on December 13, 18, 23, 31, and January 7, and of these only that taken on December 23 showed any neutralization. This sample neutralized over 75% of the virus in the test, but it is virtually certain that the antibody present came from the immune serum which had been given 18 hours previously. It is interesting that this passive antibody was no longer detectable in a sample taken on December 31, nine days after the serum had been given. Immediately after taking this sample 250 ml. of immune whole blood was given to the child and a few days later 750 mg. of gamma globulin. In spite of this the blood taken at necropsy on January 7 had no detectable antibody.

It was found that the unheated serum from the baby did not by itself neutralize variola virus and therefore lacked the natural antibody-like factor described by McCarthy and Germer (1952). The sample taken on December 18, that is before any transfusions had been given, was nevertheless able, when incorporated in virus-immune serum mixtures, to increase twentyfold the neutralization of variola virus by a heated immune serum. It therefore possessed the second or potentiating factor described by McCarthy and Germer.

Finally the vaccinia virus recovered from the bone marrow of the infant at necropsy was itself tested in neutralization tests on the chorio-allantois and shown to be readily neutralizable by anti-vaccinial rabbit serum. Further, this virus was also neutralized by serum from the two donors, serum given on December 22 (A) and blood on December 31 (M) (Table 1). The degree of neutralization of this virus did not differ from that of a stock

TABLE 1

NEUTRALIZATION TEST USING SERA FROM TWO DONORS AND NORMAL (UNVACCINATED) HUMAN SERUM AGAINST PATIENT'S VACCINIA VIRUS

Sera	Pock Counts on Individual Eggs	% of Virus Surviving
Normal human serum	20, 40, 62, 64, 65	100
Serum from donor M	6, 12, 18, 30, 54	48
Serum from donor A	9, 18, 20, 20, 25	36

strain of vaccinia virus derived by egg culture from a vaccination lesion in a normal adult (Table 2). The possibility that the virus might have become resistant to neutralization by immune sera can therefore be excluded.

TABLE 2

NEUTRALIZATION TEST USING SERA FROM TWO DONORS AND NORMAL (UNVACCINATED) HUMAN SERUM AGAINST STOCK STRAIN OF VACCINIA VIRUS

Sera	Pock Counts on Individual Eggs	% of Virus Surviving
Normal human serum	67, 79, 82, 89, 133	100
Serum from donor M	15, 29, 33, 37, 78	42
Serum from donor A	1, 7, 16, 51, 63	31

While we were preparing this paper our attention was drawn to the report by Bruton (1952) of a case of recurrent infection over a period of four years in a young boy in whom failure of antibody production was found to be associated with complete absence of gamma globulin in his serum. A specimen of serum from our case which had been obtained on December 31 (before the transfusion of whole blood) and had been stored at −78° C. for seven months was sent to Professor R. A. Kekwick for electrophoretic analysis. His report, together with normal values for newborn infants, is given in Table 3.

TABLE 3
ELECTROPHORESIS ANALYSIS

	Electrophoresis Values for E.H.	Approximate Normal Values for Newborn Infants*
Total protein	4·54 g./100 ml.	6 g./100 ml.
Albumin	52·2% of total protein	64% of total protein
Globulin		
Alpha	24·4% of total protein	13% of total protein
Beta	23·5% of total protein	10% of total protein
Gamma	0·0% of total protein	16% of total protein

* Calculated from data given by Longsworth, Curtis and Pembroke (1945)

Discussion

It has been shown that a viraemia frequently occurs after primary vaccination (Herzberg-Kremmer and Herzberg, 1930-31) and it is, therefore, not surprising that in people whose skin is already damaged by atopic eczema or other skin disease, by burns or by varicella, widespread lesions may occur. Generalized vaccinia occasionally develops in individuals whose skin was previously undamaged. The course of the disease is then very similar to smallpox, the lesions appearing in one crop about eight to 12 days after vaccination. Virus-neutralizing antibody has been demonstrated in such cases (McCarthy, 1951).

In a very few cases widespread cutaneous lesions continue to appear over several weeks; they do not go through the normal stages of development and they fail to heal. The primary lesion develops at the normal time after vaccination but also fails to heal and secondary lesions may appear around its periphery. Nearly all of these cases have been fatal.

Acland and Fisher (1893) described such a case in a 3-month-old infant vaccinated by the arm-to-arm method, the lymph being derived originally from

a calf but having had 41 human passages before this vaccination. On the fourteenth day after vaccination a large sore developed at the vaccination site and scattered lesions were present on the face, lips, trunk and extremities. Lesions continued to appear for five weeks and the child eventually died 49 days after vaccination. Throughout the course of the disease no enlargement of the lymph nodes was noted and there was little or no fever. Shortt (1933) and Dible and Gleave (1934) reported another case which was very similar to the one recorded here. The child was 3 months old and generalized lesions developed 16 days after vaccination, death occurring 10 days later. At necropsy necrotic areas were found in the liver and spleen which, on section, showed no inflammatory reaction. The histology of the skin lesions resembled that in the present case, the notable features being the absence of inflammatory reaction and the large number of cytoplasmic inclusion bodies. No antibody studies were carried out in their case. Bigler and Slotkowski (1951) described a case of generalized vaccinia in a Negro girl who had been unsuccessfully vaccinated in infancy. She was revaccinated at the age of $5\frac{1}{2}$ years on the left arm and five weeks later there was a necrotic ulcer at the vaccination site. Ten weeks after vaccination umbilicated, vesicular lesions appeared on the shoulder, back, face and hand. The left arm became gangrenous before death. Laurance, Cunliffe and Dudgeon (1952) have recorded another case in an infant of 4 months who died after a course of 89 days. In 1944 Crosbie and Downie (personal communication) saw a child who had been vaccinated at the age of 11 months and in whom lesions continued to develop until death occurred from intercurrent infection two months later. Laurance et al. (1952) mention, without giving details, two additional cases, one of which recovered. Thus of the eight cases of which we have knowledge, seven have been fatal.

The main feature which distinguishes these cases from most cases of generalized vaccinia and of eczema vaccinatum is the prolonged course, during which lesions continue to develop and fail to heal. In the course of a normal vaccination virus-neutralizing antibody appears in the blood at about 12 to 14 days and continues to rise until about three weeks when it attains a steady level. Antibody probably develops in the cells at an earlier stage at the time when the primary lesion begins to heal, i.e. about eight to nine days. In most cases of generalized vaccinia cutaneous lesions develop as a single crop about eight days after vaccination. Herzberg-Kremmer and Herzberg (1930-31) showed that the viraemia following primary vaccination usually

occurs at about the sixth to eighth day. When metastatic lesions occur they would then take another two to three days to develop. By that time the accumulation of virus-neutralizing antibody in the blood would prevent the development of further lesions and would aid the healing of those which were already present. If antibody did not develop, the viraemia would persist unchecked and the healing of metastatic lesions might be impaired. In the case reported by Laurance et al., in Crosbie and Downie's case, and in our own, failure of antibody production was demonstrated and it is probable that there was a similar failure in the other five cases listed above.

A noteworthy feature of our case was the profound lymphopenia (120 lymphocytes per c.mm.). Associated with this was the remarkable absence of lymphocytes in the sections of spleen and lymph node which were examined. Monocytes and plasma cells were present in abundance. The recent work of Fagraeus (1948) suggests that the plasma cell is the principal cell responsible for antibody production. It is, therefore, interesting that in this case failure of virus-neutralizing antibody production was associated with the presence of abundant plasma cells in the reticulo-endothelial system whereas lymphocytes were almost impossible to find. As the peripheral blood counts were only performed after the transfusion of whole blood it is possible that the scanty lymphocytes which were present in the child's blood may have been derived from the donor's blood transfused the previous day, the donor having been bled three hours before transfusion.

The complete absence of gamma globulin in the single specimen of serum that was examined is of interest in view of the report of Bruton (1952) of a child who was unable to form antibodies despite repeated exposure (both accidental and deliberate) to a variety of antigens and who was found to have a complete absence of gamma globulin in a number of specimens of serum that were examined. In our case tests against antigens other than variola virus were not made, but the complete absence of detectable neutralizing antibody for variola virus taken in conjunction with the absence of gamma globulin would suggest that the child would have been unable to form serum antibody against any other antigen.

Treatment of such cases remains unsatisfactory. In the absence of effective treatment a fatal outcome seems almost certain. Immune serum from recently vaccinated individuals has proved disappointing in the doses which have been used. We have shown that neutralizing activity rapidly diminished and after nine days was no longer detectable in the serum. It would, therefore, seem that hyperimmune animal

sera or convalescent serum from a recent case of smallpox should be given in large doses at frequent intervals. The possibility of replacement transfusions should be seriously considered if serum is not available.

Summary

A fatal case of generalized vaccinia in a baby is described. Secondary lesions developed two weeks after vaccination and fresh lesions continued to appear until death occurred five weeks later.

No neutralizing antibodies for vaccinia virus could be demonstrated in the child's serum and electrophoretic analysis showed complete absence of gamma globulin.

REFERENCES

Acland, T. D. and Fisher, C. H. (1893). *Trans. clin. Soc., Lond.*, 26, 114.
Bigler, J. A. and Slotkowski, E. L. (1951). *Pediatrics*, 7, 24.
Bruton, O. C. (1952). *Ibid.*, 9, 722.
Crosbie, W. E. and Downie, A. W. (1944). Personal communication.
Dible, J. H. and Gleave, H. H. (1934). *J. Path. Bact.*, 38, 29.
Fagraeus, A. (1948). *Acta. med. scand.*, Suppl. 204.
Herzberg-Kremmer, H. and Herzberg, K. (1930-31). *Zbl. Bakt.* 1. Abt. Orig., 119, 175.
Laurance, B., Cunliffe, A. C. and Dudgeon, J. A. (1952). *Archives of Disease in Childhood*, 27, 482.
Longsworth, L. G., Curtis, R. M. and Pembroke, R. H. (1945). *J. clin. Invest.*, 24, 46.
McCarthy, K. (1951). M.D. Thesis. Univ. Liverpool.
—— and Downie, A. W. (1948). *Brit. J. exp. Path.*, 29, 501.
—— and Germer, W. D. (1952). *Ibid.*, (In the press.)
Shortt, C. J. de Vere (1933). *Brit. med. J.*, 1, 1004.

CONGENITAL TOXOPLASMOSIS IN THE NEWBORN

BY

E. G. HALL, J. D. HAY, P. D. MOSS and M. M. P. RYAN

From the Mill Road Maternity Hospital and the Department of Child Health, the University, Liverpool

A majority of the recorded cases of congenital toxoplasmosis have shown either clinical evidence of damage to the central nervous system at birth or have developed such signs after the first few weeks of life. The purpose of this report is to describe two cases, occurring within a short period in one maternity unit, showing at birth signs of generalized disease. One infant lived only a few minutes, the other survived for several months and developed the classical picture of hydrocephalus, chorioretinitis, microphthalmia and cerebral calcification.

Case Reports

Case 1. The mother of J.M.C., a girl, first came under medical care in 1946, when her Wassermann reaction was strongly positive. She was given a full course of treatment and subsequent Wassermann reactions were all negative. At the fifteenth week of her first pregnancy in August, 1949, a precautionary course of 'novarsenobillon' and bismuth was started. After three injections penicillin was substituted for the arsenical, because of bleeding from the gums. A blood count at that time was normal. There was no history of any illness suggesting toxoplasma infection during or immediately preceding pregnancy. For the two months before delivery there was marked hydramnios. Labour occurred on February 9, 1950, a low forceps extraction being performed owing to foetal distress. The placenta weighed 740 g. (1 lb. 10 oz.) and was of normal appearance.

The infant weighed 2,730 g. (6 lb.) and was 48 cm. (19 inches) long. Her condition at birth was fairly good and she improved rapidly after aspiration of meconium from the pharynx. There was a purplish rash, suggesting small, fading, recent ecchymoses, over the trunk and limbs, but not on the hands and feet. There were no true petechiae, nor were there lesions in the mouth. The liver was slightly enlarged and the spleen easily felt. The fontanelles were large, the sutures separated, and craniotabes was present. Both eyes were small, the right more so than the left. No other abnormalities were noted.

Ten hours after birth the rash was more pronounced and there was slight jaundice. On the second day the rash had faded considerably, the jaundice had become very deep, and the fontanelle tension had increased. On the fourth day the liver was larger and hydrocephalus was evident. Ophthalmological examination by Mr. J. A. McCann confirmed the microphthalmia, the right cornea

being 6 mm. in diameter: there were extensive haemorrhagic masses in the vitreous. The left cornea was 8 mm. in diameter and there was a vitreous mass on this side also. Radiographs of the skull on February 12 and on February 23 showed multiple discrete foci of calcification arranged in linear streaks and scattered throughout the hemispheres (Fig. 1). They were most marked in the frontal area and in the region of the basal nuclei. Early hydrocephalus was present. Radiographs of the long bones, lungs and abdomen were normal.

FIG. 1.—Radiograph of the skull on February 23, 1950, to show intracerebral calcification.

The rash lasted approximately two weeks and the jaundice one month. The spleen increased in size and then diminished, but, together with the liver, remained palpable for about three months. During this period the most striking clinical feature was a rapid increase in the hydrocephalus (Fig. 2). The maximum circumference of the skull at the age of 5 months was 57 cm. (23 inches). A ventriculogram at the end of May showed an extremely thin cortex and marked internal hydrocephalus with greatly dilated lateral and third ventricles (Fig. 3). Nystagmus was constantly present and the infant appeared to be blind and mentally defective. The limbs were spastic for a time, but during the fourth month she started moving them vigorously. Her condition then

117

gradually deteriorated and she died on July 20, 1950. Sulphamezathine, 0·25 g., was given four-hourly for 11 days starting on March 6.

Investigations. These, on mother and infant, gave the following results:

MOTHER. On August 17, 1949, the blood group was O IV R with no Rh antibodies. The Kahn test was nega-

FIG. 2.—Hydrocephalus and microphthalmia: (A) on March 3, (B) on July 18.

tive. On March 8, 1950, the indirect Coombs test was negative. On March 28 a complement fixation test for toxoplasmosis was positive in a serum dilution of 1 in 40. The egg neutralization test was positive. The dye test was not done.

INFANT. On February 9, 1950, a blood count gave Hb. 18·0 g. (122% Haldane); leucocytes 9,200 per c.mm.
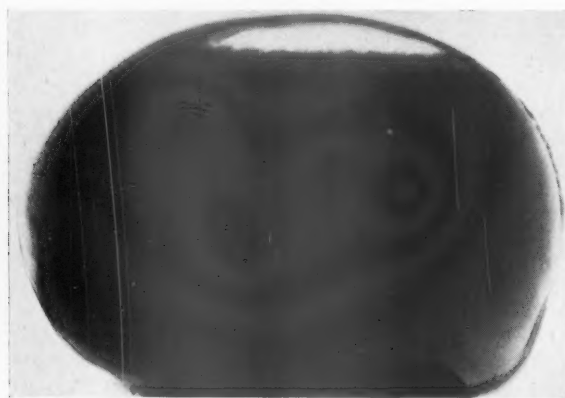

FIG. 3.—Ventriculogram taken on May 23 to show thinning of the cortex and gross dilatation of the lateral ventricles.

(differential count normal); platelets, 72,000 per c.mm.; clotting and bleeding times normal. On February 27 a complement fixation test for toxoplasmosis was positive in a serum dilution of 1 in 30. A dye test was positive (titre > 1 in 256).

On March 8 a blood count gave Hb. 13·3 g. (90% Haldane); leucocytes 8,000 per c.mm. The differential and platelet counts were normal.

On March 9 the Wassermann reaction was negative. On March 16 a blood count gave Hb. 9·6 g. (65% Haldane); leucocytes 8,000 per c.mm. (8% eosinophils).

On June 8 a complement fixation test for toxoplasmosis was positive (titre > 1 in 1,024).

On June 22 the blood group was O IV Rh positive. On the same day a biopsy of the thigh muscle was taken. Histology was normal, and *Toxoplasma* was not obtained on inoculation of mice and eggs.

The cerebrospinal fluid was examined on three occasions between the fourth and the fifteenth week, the final fluid being obtained from the ventricles. The first and last specimens were normal, but the one taken in the ninth week contained 40 lymphocytes per c.mm. and had a protein content of 200 mg.%. All three fluids were examined for *Toxoplasma* microscopically and by inoculation into mice and fertile eggs, but gave negative results.

In view of the suggestion that toxoplasmic infection might be transmitted to man from domestic animals, a complement fixation test was done on the serum of a cat in the mother's home, with a negative result.

Necropsy Report. (The necropsy was performed by Dr. R. E. Rewell who has kindly permitted us to quote from his report and has presented material to us.) The only changes outside the nervous system were early bilateral basal bronchopneumonia and slight enlargement of a rather pale liver. The bones of the vault were thin and separated. The dura and subdural space were normal. The enormous enlargement of the head was due to gross internal hydrocephalus, the cerebrospinal fluid being clear and colourless. The cerebral hemispheres were reduced to a thin layer of brain, nowhere more than 5 mm. in thickness. There were numerous areas, especially in the lateral surface of the parietal, occipital and temporal lobes, where distension was so great that the ventricular wall consisted only of a thin, translucent membrane without any gross evidence of brain tissue. The wall of the lateral ventricles was faintly granular, the choroid plexus atrophic and flattened against the thalamus. Alongside the plexus on both sides was a narrow linear zone of white calcified tissue with a smooth surface. Scattered in the cortex and the ventricular walls were scanty calcified nodules approximately 1 mm. in diameter, occurring both singly and in small groups. The third ventricle was dilated, the fourth of normal size. The basal meninges were thickened and there was a marked tonsillar pressure cone.

Histology. Numerous sections of the spleen, pancreas, ovary, stomach, duodenum, bladder, thyroid, diaphragm, thymus, adrenal and heart were examined. The appearances were normal and no *Toxoplasma* were seen. The kidney was normal except for scanty small interstitial aggregates of lymphocytes in the cortex; *Toxoplasma* were not seen. The lungs showed an early pyogenic bronchopneumonia only and the liver was of normal pattern with light periportal fatty infiltration.

BRAIN. Sections at various points in the hemispheres showed similar appearances. There were scattered cortical lesions consisting of areas of gliosis in which calcium deposits occurred as minute granules and as larger aggregates. Where these lesions reached the surface of the

FIG. 4.—Wall of the lateral ventricle (haematoxylin and eosin × 40) showing replacement of ependyma by glial tissue containing calcium deposits.

globin level was 14·8 g. (100% Haldane , her blood group O IV R, and the Kahn test was negative. Rh antibodies were absent from her serum. When questioned later she stated that there were mice in the house, and, during the early stages of pregnancy, a cat, which had since died.

She was admitted in labour on April 23, 1950, at 35 weeks' gestation, and delivery was normal. The placenta weighed 1,200 g. (2 lb. 10 oz.) and was very pale and friable, the cut surface resembling a fine-mesh latex sponge.

The infant weighed 2,170 g. (4 lb. 12 oz.) and was 42·5 cm. (17 in.) long. He was pale, oedematous, in extremely poor condition, and died 15 minutes after delivery.

The puerperium was normal. A second Kahn test on April 25 was negative, and Rh antibodies were not detected. On June 8, 1950, the toxoplasmosis complement fixation test was positive in a serum dilution of 1 in 20, and the dye test titre was 1 in 256.

A radiograph of the infant's skull, taken for reasons other than the diagnosis of toxoplasmosis, showed faint calcification in the region of the basal nuclei. As this was not seen until after the necropsy, attempts to isolate *Toxoplasma* were not made.

Necropsy. This was performed 14 hours after delivery

brain the leptomeninges were adherent and there were light perivascular aggregations of lymphocytes, monocytes and plasma cells. Frequently, however, gliosis and calcification occurred as a narrow band lying immediately beneath the surface, the overlying meninges being normal. The ependymal lining of the ventricles was replaced almost entirely by a narrow zone of compressed glia, frequently split into superficial and deep zones by microscopic calcium deposits (Fig. 4). In sections across the basal nuclei there was an almost continuous superficial zone of granular calcification, especially prominent close to the choroid plexuses where macroscopic deposits were frequent (Fig. 5). The choroid plexus of the lateral and third ventricles showed only a mild fibrosis of the stroma. Sections of the midbrain showed a normal pattern. The aqueduct in its proximal portion was dilated, and its ependyma largely intact. There were, however, small nodules of gliosis encroaching on the lumen, by-passing and isolating clumps of ependymal cells. At the level of the inferior quadrigeminal body, extensive gliosis reduced the lumen to a minute channel (Fig. 6). The fourth ventricle, cord and cerebellum were normal. Very scanty pseudocysts were seen in the brain stem.

The eyes were not available for examination.

PLACENTA. Two blocks were available for study. Numerous sections did not show any structural abnormality, nor were any parasites seen.

The mother of J.M.C. became pregnant again, and gave birth to a mature normal infant in August, 1951.

Case 2. The mother of Baby S. was 37 years old and had had six previous pregnancies. The eldest child died of diabetes, but the other children were well. In none had jaundice been noted during the neonatal period. The mother was first seen on November 31, 1949, at approximately 14 weeks' gestation. She gave no history of illness during or immediately before pregnancy. Her haemo-
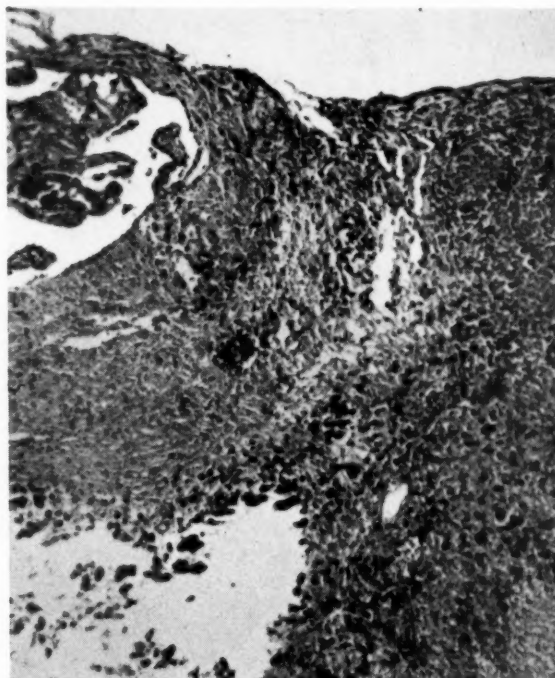

FIG. 5.—Wall of the lateral ventricle (haematoxylin and eosin × 65) showing extensive necrosis and granular calcification close to the choroid plexus.

by one of us (P.D.M.) Externally, the child showed marked generalized oedema, faint jaundice and extreme pallor. There was a purpuric generalized rash, most profuse on the face and scanty on the soles and palms. On the trunk there was an average of six lesions per 100 cm²., the individual haemorrhages varying from pin-point size to 3 mm. diameter. The eyes appeared normal and there was no external evidence of hydrocephalus.

Internally, the fatty tissues were jaundiced and the body-wall oedematous. Petechiae were seen in the muscles, especially of the legs.

There was a very small amount of free fluid in the pleural cavities, but no pleural petechiae. The lungs (27 g.) were small and unexpanded. There was free fluid in the pericardium.

The chambers of the heart were dilated; the myocardium was pale. There were no petechiae.

FIG. 6.—Aqueduct at the level of the inferior quadrigeminal body (haematoxylin and eosin × 55) showing gliosis.

In the abdomen there was approximately 40 ml. of straw-coloured fluid.

Discrete and confluent petechiae were seen at the upper end of the oesophagus. Occasional mucosal and subserous petechiae were seen in the stomach and small intestine.

The colon was normal.

The liver (160 g.) was enlarged, pale and yellow.

The spleen (68 g.) was also enlarged, dark purple and firm. There was nothing of note in the endocrine glands.

The kidneys (44 g.) were enlarged, with subcapsular petechiae, a smooth surface, the cortex intensely congested to within 1 mm. of the surface and the medulla relatively pale. Nothing was noted in the urinary passages.

The skull was of normal size. The bones were normal. There was a small tear in the falx just above the tentorium, with a little blood clot in the posterior fossa. The brain had a normal surface configuration. There was no hydrocephalus. Scattered over the surface, and particularly within the sulci, were minute yellow, discoloured zones in the superficial cortex, nowhere more than 0·5 mm. in depth, to which the leptomeninges were adherent. The lining of the lateral ventricles was granular and yellow, the zone of discoloration extending about 0·5 mm. into the surrounding brain, which otherwise appeared normal. Sections across the brain-step and basal nuclei were normal. There was slight granularity of the floor of the fourth ventricle.

Histology. The portal areas of the liver (Fig. 7) were densely infiltrated with mononuclear cells, lymphocytes, plasma cells and occasional eosinophils, the infiltrate extending between compressed and distorted liver columns into the lobules. There was early fibrosis extending from the portal tracts. The sinusoids were widely dilated and islands of extramedullary erythropoiesis were frequent. Biliary plugs were present in the canaliculi, but the bile ducts were normal. Though no pseudocysts were seen, there were small groups of spherical or ovoid bodies, resembling free *Toxoplasma*, amongst the inflammatory cells. There was a marked excess of iron pigment.

In the spleen follicles were inconspicuous. The pulp was congested and densely packed with erythropoietic cells and mononuclear cells. Erythrophagocytosis was present. No pseudocysts or free *Toxoplasma* were seen. Much free iron was present.

The lungs were not aerated. There were scanty meconium granules. In the interstitial tissue, especially around the bronchi and blood vessels, there were occasional mononuclear cells. In the alveoli there were scattered mononuclear cells. In some of these and in the interstitial tissue parasites were seen singly and in groups (Fig. 8).

In the skeletal muscle of the calf there was diffuse mononuclear and lymphocytic infiltration, especially marked in perivascular areas, many capillaries having dense collars of cells. There was a moderate degree of oedema. Occasional areas of necrosis of muscle fibres with surrounding zones of inflammatory cells were seen. As well as small groups of free parasites, occasional large pseudocysts in parasitized fibres, without cellular reaction, were seen. Throughout both cortex and medulla of the kidney, but especially in the former, there was a dense infiltration of mononuclear cells, plasma cells and lymphocytes, with numerous foci of erythropoiesis. Areas of haemorrhage and necrosis were frequent. The glomeruli were normal, but the convoluted tubules were distorted and compressed by the interstitial cellular reaction. There was a similar cellular infiltration in the
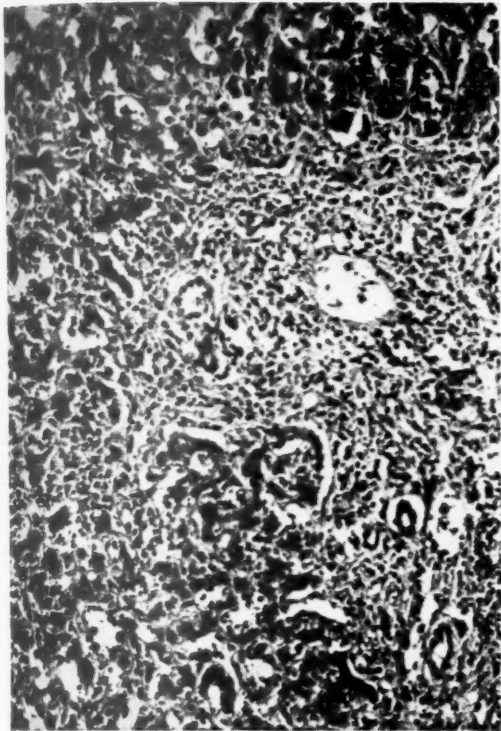
FIG. 7.—Liver (haematoxylin and eosin × 100), showing infiltration and fibrosis of portal tracts, with sinusoid erythropoiesis.
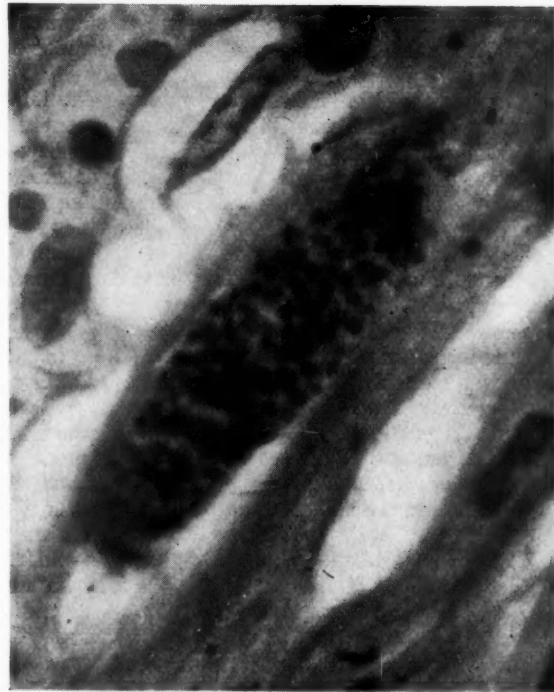
FIG. 9.—Heart (haematoxylin and eosin × 1,800) showing pseudocyst in muscle fibre without surrounding reaction.
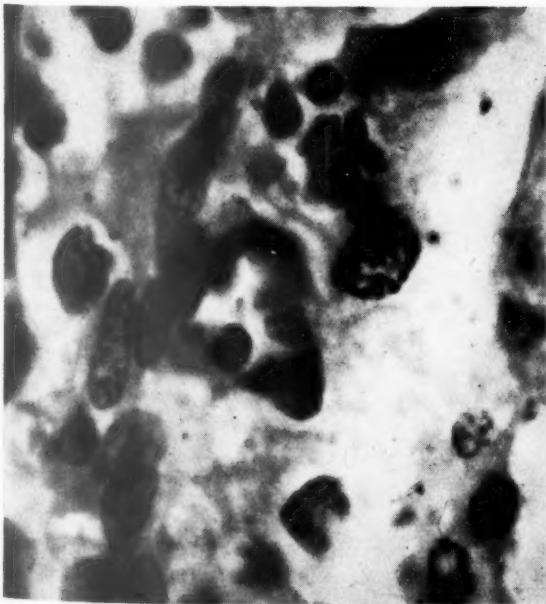
FIG. 8.—Lung (haematoxylin and eosin × 1,300) showing intracellular mass of parasites in alveolar wall and nucleated red cells in capillaries.

FIG. 10.—Brain (haematoxylin and eosin × 36) showing necrotic cortical lesion, prominent marginal capillaries and meningeal infiltration.

peripelvic connective tissue. Granules of iron pigment were conspicuous in the renal tubular epithelium. No definite free parasites were seen nor were pseudocysts noted.

The pattern of the pancreas was normal. The interlobular stroma was oedematous. Scattered throughout were numerous foci of erythropoiesis, lymphocytes, histiocytes and plasma cells. The peripancreatic areolar tissue showed similar diffuse infiltrations. No *Toxoplasma* were seen.

The bone marrow was extremely cellular containing a high proportion of erythroid cells. Platelet precursors were relatively scanty. Occasional small groups of *Toxoplasma* were seen.

In the heart oedema was marked with diffuse inflammatory infiltration and islands of erythropoiesis. Occasional muscle fibres contained pseudocysts, without surrounding reaction (Fig. 9).

Some of the villi of the placenta showed a moderate degree of oedema, with scanty large mononuclears and plasma cells. In the villi, both within mononuclear cells and lying freely, were *Toxoplasma* singly and in small clumps. When single, they were predominantly ovoid, the cytoplasm staining bluish-red with haematoxylin and eosin, the nuclear chromatin, usually towards one end of the organism, a darker blue. When in clumps, the nuclear chromatin showed as round blue areas, frequently surrounded by a pale zone, the cytoplasm being ill defined. Nucleated red cells were present within the capillaries of the villi.

The superficial cortical lesions noted macroscopically on the brain were areas of necrosis containing many compound granular corpuscles and much nuclear debris. At their margins there was a zone of prominent, dilated capillaries, with swollen endothelial cells and narrow cuffs of reticulum and plasma cells (Fig. 10). Similar cells were present throughout the marginal zone. In the most recent lesions, where necrosis was minimal and the cellular infiltration most dense, free *Toxoplasma* and small pseudocysts were seen, but in the older lesions calcification in minute granules made certain identification of the parasites difficult and sometimes impossible. The adherent overlying meninges were congested and infiltrated with plasma cells, lymphocytes, large mononuclear cells and occasional polymorphs, the infiltration extending for some distance over uninvolved cortex. *Toxoplasma* were seen in small numbers lying free in the subarachnoid space, and within mononuclear and capillary endothelial cells.

In the walls of the lateral ventricles there were extensive areas in which the ependyma was replaced by confluent areas of necrosis similar to those on the surface, profusely studded with dust-like particles of calcium. Between the necrotic areas the ependyma was broken up and covered with an organizing fibrillary membrane containing isolated inflammatory cells. Similar changes were present in the third ventricle, necrosis and calcification being most advanced close to the choroid plexus.

The aqueduct was patent throughout, but its lumen was slightly reduced by glial nodules which erupted through and isolated small groups of ependymal cells.

Similar glial nodules, but no areas of necrosis, were seen in the floor of the fourth ventricle (Fig. 11).
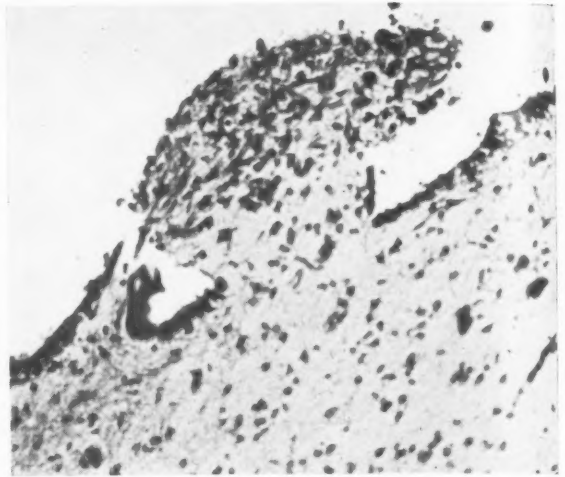
FIG. 11.—Brain (haematoxylin and eosin × 130) showing glial nodule in floor of the fourth ventricle.

The deeper parts of the brain showed only scattered miliary granulomas and occasional pseudocysts, the latter devoid of surrounding reaction (Fig. 12).
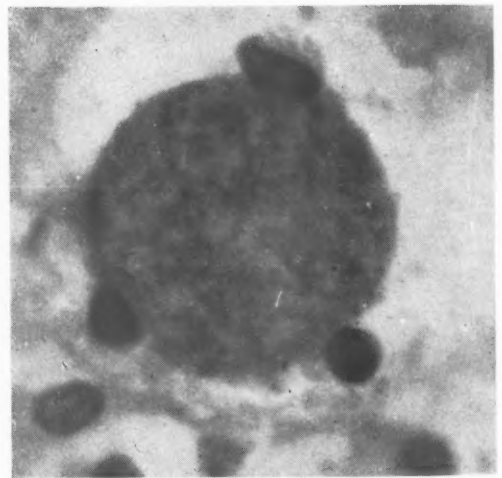
FIG. 12.—Brain (haematoxylin and eosin × 1,700) showing typical pseudocyst.

The eyes were not available for examination.

This case showed a close clinical resemblance to haemolytic disease of the newborn, but histological examination revealed widespread neural and extraneural infection by *Toxoplasma*. Serological examination of the mother's serum supported this diagnosis, and did not show evidence of iso-immunization.

Discussion

We do not propose to discuss the commoner clinical features or the specific pathological lesions of congenital toxoplasmosis as these have been reviewed recently by Callahan, Russell and Smith (1946), Binkhorst (1948), Magnusson and Wahlgren (1948), Frenkel (1949), Wyllie and Fisher (1950) and Hart, Paulley, Rivers and Westlake (1951). There are, however, several points worthy of comment.

The rash was an arresting clinical feature of both our cases. Rashes have been mentioned in a number of the published cases, but not always described in detail. Callahan *et al.* described the rash in two of their cases as ecchymotic. Most of the others are described as petechial or purpuric, sometimes coming on after birth and noted especially in cases with jaundice. The usual distribution has been that seen in our cases. Several factors may play a part in their production. Hypoprothrombinaemia has been noted, especially with jaundice, so that liver damage may be a major factor, especially in those cases where the rash appears shortly after birth. A low platelet count has also been recorded in one or two cases and platelet deficiency due to toxic effects on the bone marrow has to be considered. We have seen a similar rash in congenital thrombocytopenic purpura. In our Case 1 there were 72,000 platelets per c.mm. on the day of birth, the bleeding and clotting times being normal. At 4 weeks old the platelet count was normal. In our Case 2, showing a similar rash, the bone marrow was very active, but platelet precursors were scanty. In the few previous reports a cellular marrow has been noted, but no comment made on platelet formation. It is possible that the skin lesions might also be produced by embolism during the parasitaemic stage, or by a local allergic reaction to the presence of *Toxoplasma* in capillary endothelial cells.

Congenital toxoplasmosis may closely resemble haemolytic disease of the newborn, as in Case 2, where the initial clinical diagnosis, based on the gross pallor, universal oedema and enlargement of liver and spleen, was hydrops foetalis. A similar diagnosis of erythroblastosis was made in three of the 18 cases reviewed by Callahan *et al.* (1946), in the case reported by Harwin and Angrist (1948) and in one of the cases reported by Magnusson and Wahlgren (1948).

In these cases and in other infants dying within a few days of birth (e.g. Pratt-Thomas and Cannon, 1946; Werthemann, 1948), extramedullary erythropoiesis of abnormal degree has been observed, usually associated with jaundice and enlargement of the liver and spleen. Though data regarding blood group incompatibility are not available, except in

our Case 2 and in that reported by Smitt and Winblad (1948), it would seem more reasonable to regard this high incidence of abnormal erythropoiesis as due to infection by *Toxoplasma* rather than to the simultaneous occurrence of two diseases. It is well known that anaemia with extramedullary erythropoietic activity is a common result of severe infection in the young infant. Such a response would be expected more frequently in recent infection of the foetus during the parasitaemic stage ('acute toxoplasmosis' of Frenkel, 1949), rather than in the later phase when active disease is limited to the central nervous system ('subacute toxoplasmosis') and other organs are normal or show evidence of past infection only. A survey of published necropsy reports indicates that, in general, the greater degrees of extramedullary erythropoiesis are associated with evidence of severe generalized disease, changes in the central nervous system in some instances being relatively early, while in those with little or no abnormal extramedullary erythropoiesis, extraneural disease is overshadowed by severe involvement of the brain and cord.

Callahan *et al.* (1946) remark that there is, in most cases, no satisfactory explanation of jaundice occurring in congenital toxoplasmosis. In the liver, toxoplasmic granulomas have not been found, and free parasites noted only on very rare occasions, the main features, except in one case discussed below, being foci of erythropoiesis, haemosiderosis, inspissation of bile within the canaliculi, and occasionally a mononuclear periportal reaction. In cases of this type surviving beyond the immediate post-natal period (Zuelzer, 1944, cases 2 and 3; Cowen, Wolf and Paige, 1942; Paige, Cowen and Wolf, 1942; Magnusson and Wahlgren, 1948, case I; Smitt and Winblad, 1948) the clinical evidence has been compatible with hepatitis. Post-mortem studies in three such cases (Smitt and Winblad, 1948; Werthemann, 1948; Zuelzer, 1944) demonstrated hepatitis with definite fibrosis in two. Again, no specific lesions of toxoplasmosis were demonstrated. Our case 2, where the initial clinical diagnosis was hydrops foetalis, showed severe hepatitis with fibrosis at birth, and resembled case 11 of Magnusson and Wahlgren, a hydropic infant dying one minute after birth, where there was a well marked centrilobular hepatic necrosis.

The only regular findings in the enlarged spleens have been excessive haemopoietic activity and haemosiderosis. In the few instances where bone marrow has been sectioned haemopoietic activity has been normal or increased.

Sabin (1942) suggested that the jaundice might be due to a direct toxic effect of *Toxoplasma* on the liver

cells. Such a mechanism is possible, but the evidence detailed above suggests that it may be due, at least in part, to rapid destruction of red cells and liver damage similar to that seen not uncommonly in haemolytic disease due to iso-immunization.

Observations on the placenta in toxoplasmosis are very scanty. In a majority of cases it is not mentioned: in a few it is reported as macroscopically normal, without further details being given. Lelong, Rossier, Alison, Le Tan Vinh, Desmonts, Boulard and Ribierre (1948) describe two cases; in one the infant weighed 2,550 g. (5 lb. 9 oz.) and the placenta 650 g. (1 lb. 7 oz.); in the other the weights were, respectively, 3,000 g. (6 lb. 9 oz.) and 500 g. (1 lb. 2 oz.), both within normal limits for the maturity of the infants. The placentas are not further described. In neither case is there any note of jaundice, hepato- or spleno-megaly or rash during the neonatal period. In the case described by Kean and Grocott (1948) the placenta was noted to be very grey, but unfortunately could not be further examined. The patient of Smitt and Winblad (1948), similar in many respects to our first case, weighed 2,460 g. (5 lb. 6 oz.) at birth, the placenta 880 g. (1 lb. 15 oz.). Paige *et al.* (1942) describe a placenta, apparently grossly normal, in which microscopy showed only evidence of secondary pyogenic infection.

Mellgren, Alm and Kjessler (1952) have recently described a placenta in which there were areas of necrosis infiltrated with polymorphs, and showing early calcification. Bodies resembling *Toxoplasma* were seen, especially at the margins of the infarcts, and *Toxoplasma* were subsequently cultured from the vaginal discharges. Serological tests on the mother were positive. The moderately macerated, immature infant did not show any gross lesions at necropsy, and sections of the lungs did not reveal *Toxoplasma*.

In our case 1 the weight of the placenta was somewhat greater than the average for the weight and maturity of the infant, but in case 2 it was more than half the weight of the baby and had the grey appearance noted by Kean and Grocott (1948).

In both cases studied by us there was no evidence of a gross inflammatory reaction in the placenta, the changes being confined to slight cellular infiltration and oedema in case 2. Though bodies resembling *Toxoplasma* were infrequently seen in the placenta of case 2, they were devoid of tissue reaction and were probably derived from the foetal parasitaemia, rather than directly from the mother. Focal areas of necrosis similar to those described by Cowen and Wolf (1950) in the placentas of experimentally infected mice were not seen. If such lesions do occur during transmission of infection from mother to foetus it is quite possible that they may be un-identifiable by the time gross lesions have been produced in the infant. Werthemann (1948), in commenting on the absence of placental damage in cases of toxoplasmosis, says that a similar state of affairs exists in congenital malaria, where, though *Plasmodia* may be found in the placenta in large numbers, there is little evidence of tissue reaction.

It has been suggested that the malarial parasite may be able to gain access to the foetal circulation without structural damage to the placenta. An alternative suggestion is that small haemorrhages in the placenta during malarial rigors or during labour may occur. We think, therefore, that it is improbable that structural changes in the placenta directly due to toxoplasmosis would account for the considerable enlargement of the placenta in our case 2 or for the slighter enlargement in our case 1 and in the case of Smitt and Winblad (1948). It appears more probable that the increase in placental size was due to oedema, analogous to that occurring in hydrops foetalis.

Summary

The clinical, morbid anatomical and histological details of two cases of congenital toxoplasmosis presenting somewhat unusual features at birth are described. *Toxoplasma* were identified in both cases. The significance of some of the extraneural lesions is discussed, and the absence of specific changes in the placentas noted.

REFERENCES

Binkhorst, C. D. (1948). *Toxoplasmosis.* Leiden.
Callahan, W. P., Russell, W. O. and Smith, M. G. (1946). *Medicine, Baltimore*, 25, 343.
Cowen, D. and Wolf, A. (1950). *J. exp. Med.*, 92, 403.
—— —— and Paige, B. H. (1942). *Arch. Neurol. Psychiat., Chicago*, 48, 689.
Frenkel, J. K. (1949). *J. Amer. med. Ass.*, 140, 369.
Hart, E. W., Paulley, J. W., Rivers, J. S. and Westlake, E. K. (1951). *Arch. Midd. Hosp.*, 1, 26.
Harwin, M. and Angrist, A. (1948). *Arch. Pediat.*, 65, 124.
Kean, B. H. and Grocott, R. G. (1948). *J. Amer. med. Ass.*, 136, 104.
Lelong, M., Rossier, A., Alison, F., Le Tan Vinh, Desmonts, G., Boulard, —. and Ribierre, —. (1948). *Arch. franç. Pédiat.*, 5, 113.
Magnusson, J. H. and Wahlgren, F. (1948). *Acta. path. microbiol. scand.*, 25, 215.
Mellgren, J., Alm, L. and Kjessler, Å. (1952). *Ibid.*, 30, 59.
Paige, B. H., Cowen, D. and Wolf, A. (1942). *Amer. J. Dis. Child.*, 63, 474.
Pratt-Thomas, H. R. and Cannon, W. M. (1946). *Amer. J. Path.*, 22, 779.
Sabin, A. B. (1942). *Advanc. Pediat.*, 1, 1.
Smitt, O. and Winblad, S. (1948). *Acta path. microbiol. scand.*, 25, 585.
Werthemann, A. (1948). *Ann. paediat., Basel*, 171, 187.
Wyllie, W. G. and Fisher, H. J. W. (1950). *Quart. J. Med.*, 19, 57.
Zuelzer, W. W. (1944). *Arch. Path., Chicago*, 38, 1.

MANDIBULOFACIAL DYSOSTOSIS IN AN AFRICAN INFANT

BY

SAMUEL WAYBURNE

From the Department of Paediatrics, Baragwanath Hospital and University of the Witwatersrand, Johannesburg

Under the title of 'mandibulofacial dysostosis' Franceschetti and Klein (1949) described a comparatively uncommon but easily recognizable condition, tending to appear in families and showing an irregular dominant mode of inheritance. Berry (1889) first recorded the condition in a mother and her daughter. Most of the descriptions have appeared in the Continental and American literature*. As far as can be ascertained this is the first description of the fully developed syndrome in an African Negro.

The salient features of this type of dysostosis are (1) palpebral fissures sloping downwards and laterally ('antimongoloid') with a coloboma in the outer portion of the lower lids and, more rarely, in the upper lids; (2) hypoplasia of the facial bones, especially the malar bones and the mandible; (3) malformation of the external ear and, occasionally, of the middle and inner ears; (4) macrostomia, high palate, abnormal position and malocclusion of the teeth; (5) blind fistulae situated between the angles of the mouth and the ears; (6) a tuft of hair extending towards the cheeks; (7) other associated anomalies such as facial clefts and further skeletal deformities.

Case Report

S.N., an African boy aged 5 weeks, was admitted to the Paediatric Department of Baragwanath Hospital on August 29, 1951. The main complaints were of difficulty in breathing since birth and loss of weight. Pregnancy and labour had been normal, and the mother denied any illness during gestation. The baby took the breast and also received complementary feeds of sweetened condensed milk. In spite of the breathing difficulty he had sucked well, but sleep had been erratic and poor. There was no history of diarrhoea or vomiting. The birth weight was unknown. There was one 4-year-old normal sibling. The mother was quite well, but the father had been completely deaf since childhood. The parents appeared to be of normal intelligence.

* The condition is often referred to as the Treacher-Collins syndrome (Collins, E. T. (1900), *Trans. ophth. Soc.*, **20**, 190).—ED.

Examination revealed a cold, cyanosed, extremely wasted, dehydrated baby, weighing 5¼ lb., breathing with great difficulty and showing marked rib recession. A peculiar facies was immediately noted. The face was very narrow, the palpebral fissures sloped downwards and outwards, and there was a coloboma in the lateral part of each lower lid. The jaw was very small, while the mouth and tongue were large, the latter falling back into the pharynx and causing respiratory obstruction. The pinnae were markedly deformed and just anterior to the upper part of each was a small, blind fistula. The tympanic membranes were normal. There was a depression in the

FIG. 1.   FIG. 2.

FIG. 1.—Macrostomia, downward and outward obliquity of the palpebral fissures, and deformity of the pinna.

FIG. 2.—Micrognathia; deformity of pinna with adjacent fistula; depression in region of malar bones with small tuft of hair.

region of each zygoma, from which grew a tuft of fine hair.

The baby was resuscitated by intravenous therapy, followed by nasal tube feeds and in three to four days was able to take the bottle. Great care had to be taken in positioning him, otherwise respiratory obstruction recurred.

Further investigation revealed normal ocular fundi and negative serological tests for syphilis.

Discussion

The features shown by this baby are typical of the syndrome described by Franceschetti and Klein (1949). They stated that there was in their cases a disturbance of development and ossification of the facial bones dating from the end of the second month of gestation. They quoted numerous family histories of affected parents and children and some of their near relations including the families of six cases of their own. Several of the affected patients died in the first six months of life (Debusmann, 1940). The frequency of infantile mortality amongst the siblings and relatives of Franceschetti and Klein's patients was found to be very high.

It has also been found that there are sometimes associated anomalies such as atresia of the lacrimal duct and ectropion, complete atresia of the external auditory canal and inner ear deformities.

McEnery and Brennemann (1937) described a series of five cases with similar features, some being unilateral. They quoted as characteristic findings the presence of cleft lip or cleft palate, defective zygomatic arch, a sharp angular or downward depression of both lower lids, microphthalmos, deformity of one or both ears and a tendency to mental retardation. They gave an embryological description from the work of Blair and Brown (1938) stating that:

'Congenital deformities of the mouth and face are most frequently related to some abnormality of development or closure of the embryonal fissures, but there are many other types of deformities that do not have as definite a basis of origin.'

The latter authors give a photograph and description of a child with obvious manifestations of the syndrome and regard this particular child as suffering from an unclassified type of gross deformity that may be associated with cleft palate, deformity or absence of ears, deformity of the nose and microphthalmia.

Franceschetti and Klein divide their own and reported cases into complete, incomplete, abortive, unilateral and atypical forms, and stress the diagnostic importance of the slope of the eyes and coloboma of the lower lids. One of the patients discussed by them was a 3-year-old Negro girl described by Leopold, Mahoney and Price (1945). She showed an incomplete form of the syndrome, the chief features being the downward obliquity of the palpebral fissures with coloboma of the lower lids, although the ears were normal. The mother and maternal grandfather of this child showed downward obliquity of the palpebral fissures and all three of them showed bilateral absence of the zygomatic processes of the temporal bones. Three other members of the family were also reported as having been affected.

The only abnormality ascertained in the family history of our patient was the father's deafness, a condition present since his childhood. His external ears showed no deformity, but the tympani were sclerosed and retracted. His speech, however, was normal, indicating that his deafness was probably acquired. Full auditory examination was not carried out. No history of mental defect or congenital abnormality in any other member of the family was admitted. It should be noted that the illiterate parents of the child were so unobservant that apparently they had not noticed the facial anomalies.

Subsequent attempts to follow the child's development were unsuccessful, and it was reported that the infant succumbed at the age of 3 months, the cause of death being unknown.

Summary

A case of mandibulofacial dysostosis in a baby of pure African origin is presented. The child showed the typical obliquity of the eyes with coloboma of the lower lids, hypoplasia of the facial bones and mandible, macrostomia, blind fistulae anterior to the pinnae and tufts of hair over the region of the hypoplastic zygomatic arches.

The literature is reviewed and the aetiology discussed.

REFERENCES

Berry, G. A. (1889). *Roy. Lond. opthal. Hosp. Rep.*, 12, 255; quoted by Franceschetti and Klein.
Blair, V. P. and Brown, J. B. (1938). In Brennemann, J., *Practice of Pediatrics*, vol. 3, ch. 1. Hagerstown, Md.
Debusmann, —. (1940). *Arch. Kinderheilk.*, 120, 133; quoted by Franceschetti and Klein.
Franceschetti, A. and Klein, D. (1949). *Acta ophthal. Kbh.*, 27, 143.
Leopold, I. H., Mahoney, J. F. and Price, M. L. (1945). *Arch. ophthal. Chicago*, 34, 210.
McEnery, E. T. and Brennemann, J. (1937). *J. Pediat.*, II, 468.

NEONATAL DIPHTHERIA

BY

MICHAEL CURTIN

From the Child Health Clinic, City Hall, Cork

Several outbreaks of nasal and nasopharyngeal diphtheria in infants aged under 1 month have been recorded. O'Regan, Heenan and Murray (1943) described three separate outbreaks in a foundling hospital in Tipperary during the years 1937-41. Thirty-six infants aged under 1 month were infected and 23 died. Rolleston (1910) referred to similar outbreaks of neonatal diphtheria described in Paris and Vienna in the years 1877-87. Liakka (1947) in Finland reported 31 cases of diphtheria in the new-born with a 30% mortality, and Parish (1949) referred to local epidemics reported from Norway and Sweden. Isolated cases of neonatal diphtheria, however, are not common. Grant (1952) found only one case amongst 2,986 diphtheria admissions to Sheriff Hill Infectious Diseases Hospital, Gateshead, during the decade 1936-46, and Rolleston (1910) observed that there were only four infants aged under 2 months amongst 7,285 cases of diphtheria admitted to Grove Hospital, London.

Primary faucial diphtheria is rare during the neonatal period. McSweeney (1952) found no case of faucial diphtheria in this age group in 8,746 diphtheria cases admitted to Cork Street Fever Hospital, Dublin, in the years 1934-46 and Grant (1952) found no case of this nature in his series. The following case report of faucial diphtheria in an infant aged 22 days may therefore be of interest.

Case Report

F.C., a seventh born boy, was first seen at the Child Health Clinic, Cork, when he was 22 days old. The infant was breast fed and had progressed normally until he attained the age of 20 days. The mother then noted that he became increasingly lethargic and refused to take the breast.

On examination the infant was pale and apathetic and his cry was weak. A grey membrane covered the left tonsil, extended backwards over the posterior faucial pillar and also encroached on the anterior faucial pillar. The membrane was adherent to the underlying tissues and swabbing resulted in bleeding. There was no nasal discharge and no evidence of nasal block. The infant weighed 6 lb. 12 oz. and his temperature was 97·8° F.

A clinical diagnosis of diphtheria was made and accordingly 20,000 units of antitoxin were given pending bacteriological confirmation.

On the following morning a throat swab was reported positive for *C. diphtheriae*, which on further investigation proved to be gravis in type and virulent on guinea-pig inoculation. The infant was admitted to hospital and a further 40,000 units of antitoxin were administered. On admission he was also given 500,000 units of penicillin followed by 100,000 units four-hourly. On his third day in hospital the infant suddenly collapsed due to vascular failure and was revived with difficulty. Two days later palatal paralysis with nasal regurgitation developed and this necessitated oesophageal feeding for three weeks.

Convalescence was complicated by acute otitis media but was otherwise uneventful and the infant was discharged after 164 days in hospital.

Epidemiology. All contacts were swabbed and virulent gravis-type organisms were isolated from a brother of the patient. This boy, who was aged 14 years, proved to be a symptomless faucial carrier. On questioning him it was discovered that he had prepared a feed of sugar and water two days before the baby fell ill, and before offering this bottle to the infant he sucked the teat to satisfy himself that the contents were satisfactory. He was later admitted to hospital where, despite intensive treatment with penicillin, the carrier state persisted for four months but subsequently cleared following tonsil-lectomy.

The level of antitoxin in the mother's blood was found to be less than 0·001 units per ml. while the level in the case of the carrier was 10 units per ml.

Comment

It has long been recognized that a mother transmits diphtheria antitoxin to her infant. Andrewes, Bulloch, Douglas, Dreyer, Gardner, Fildes, Ledingham and Wolf (1923) reviewed the early work of Polano (1904) and Kayser (1905) who found that the antitoxin titres of a mother and her newborn infant closely corresponded. Later von Groër and Kassowitz (1915) showed that the correspondence was not always exact, and they suggested that in some cases the placenta may hold back or selectively transmit the circulating antitoxin. This hypothesis has received additional support from the work of

Barr, Glenny and Randall (1949) who found that in some cases the antitoxin content of cord blood was double that of mother's blood. Even allowing for selective transmission of antitoxin in some cases, it follows that in a given area the percentage of infants born with an adequate level of circulating antitoxin will depend on the immunity of the adult population. This in turn depends on such factors as the density of the population and the amount of natural and artificial immunization in the area. Thus while von Groër and Kassowitz (1915) in Vienna found that 84% of cord bloods contained 0·005 units or more of antitoxin per ml. Randall (1949) found this level in only 70% of cord bloods in one area in London, and Barr, Glenny and Parish (1951) have recently found much lower figures in several areas in Britain.

While it has been shown that a varying percentage of infants are protected from diphtheria at birth by a blood antitoxin titre of 0·005 u./ml. or more it cannot be assumed that this protection is complete. Ipsen (1946) doubted whether any level of antitoxin gives complete assurance against infection and Hartley, Tulloch, Anderson, Davidson, Grant, Jamieson, Neubauer, Norton and Robertson (1950) showed that 36% of persons admitted to hospital with diphtheria had a blood antitoxin titre of 0·005 u./ml. or more. It should also be noted that the antitoxin levels in these persons were indicative of a previously stimulated immunizing mechanism, and it is doubtful if similar levels obtained by placental passage would afford comparable protection. In this respect it is of interest that O'Regan and others (1950) Schick-tested six mothers whose infants developed diphtheria between the eighth and the twenty-seventh day after birth and found that all six mothers were negative to the Schick test.

In any case the protection afforded by circulating antitoxin is rapidly lost by the majority of infants during the weeks following birth. Barr and others (1949) found that the average antitoxin content of the serum of babies 10 days old was half that of cord blood and that subsequently babies lost half their antitoxin every four and a half weeks. There is, however, some evidence that antitoxin levels are better maintained in the case of breast-fed infants (von Groër and Kassowitz, 1919).

It has frequently been suggested that young infants may also be protected from diphtheria by local tissue immunity but the part which this plays is difficult to assess.

The 'isolation of infancy' is an important protective factor and may well explain the comparative rarity of sporadic cases of neonatal diphtheria. Since newborn infants are generally considered to be immune it is possible that isolated cases may be missed, especially as the disease at this age is usually nasal or nasopharyngeal in type. It has been suggested that the rarity of faucial diphtheria is due to the acid reaction of the mouth and the poor development of the tonsils in early infancy. In the case described infection by fomite transmission may have occurred and this might explain why the initial site of infection was in the fauces.

When an outbreak of neonatal diphtheria occurs in an institution all newborn infants should be given a prophylactive dose of diphtheria antitoxin. Reliance should not be placed on antitoxin administered to the mother before the infant's birth, as Chesney (1945) and Hartley (1948) have shown that heterologous antitoxin does not readily pass the placental barrier.

Before methods of protecting neonatal infants in general against diphtheria can be discussed the incidence of the disease in infants aged under 1 year must be considered. Gaffney (1943) showed that 8·1% of those dying from diphtheria in Dublin during the years 1936-42 were under 1 year of age and even higher figures have been found in other areas. Thus the active immunization of infants should be begun at as early an age as practicable. Young infants withstand immunization well but Vahlquist (1949) and Barr and others (1950) have shown that a passive antitoxin concentration exceeding 0·1 u./ml. interferes with active immunization.

It has been suggested that expectant mothers should be actively immunized during the early months of pregnancy so that their infants would be born with a high titre of circulating antitoxin. While this procedure would probably afford neonatal infants a considerable degree of protection it might well interfere with early active immunization. It is tentatively suggested that it may be advisable to rely on the 'isolation of infancy' to protect neonatal infants especially since this factor probably operates most strongly during the first month of life. At the end of the first month active immunization might be begun using 0·5 ml. (25Lf) P.T.A.P. to be followed by two injections of similar dosage during the first year. Admittedly the suggested dosage is high but in a proportion of cases the initial dose will be ineffective because of residual passive immunity. The disadvantage of having to give three injections is counterbalanced by the introduction of combined antigens.

No hard and fast rules can be laid down for the immunization of young infants until an answer is obtained to many of the problems which still surround neonatal diphtheria. Not the least of these is the role played by breast feeding in the maintenance of passive immunity.

Summary

A case of faucial diphtheria in an infant aged 22 days is described.

Reference is made to epidemics of neonatal diphtheria and to the incidence of isolated cases.

Factors which contribute to the low incidence of sporadic cases of neonatal diphtheria are mentioned.

The problem of protecting infants against diphtheria during the neonatal period and the early months of infancy is discussed.

REFERENCES

Andrewes, F. W., Bulloch, W., Douglas, S. R., Dreyer, G., Gardner, A. D., Fildes, P., Ledingham, J. C. G. and Wolf, C. G. L. (1923). *Diphtheria.* Med. Res. Coun. Lond., p. 288.
Barr, M., Glenny, A. T. and Parish, H. J. (1951). *Lancet,* 1, 713.
—— —— and Randall, K. J. (1949). *Ibid.,* 2, 324.
—— —— —— (1950). *Ibid.,* 1, 6.
Chesney, G. (1945). *Monthly Bull. Minist. Hlth. Lond.,* 4, 144.
Gaffney, J. C. (1943). *Irish J. med. Sci.,* No. 208, p. 97.
Grant, J. (1952). Personal communication.
Groër, F. von and Kassowitz, K. (1915). *Z. ImmunForsch.,* 23, 108.
—— —— (1919). *Ibid.,* 28, 327.
Hartley, P. (1948). *Monthly Bull. Minist. Hlth. Lond.,* 7, 45.
——, Tulloch, W. J., Anderson, M., Davidson, W. A., Grant, J., Jamieson, W. M., Neubauer, C., Norton, R. and Robertson, G. H. (1950). *Spec. Rep. Ser. med. Res. Coun. Lond.,* No. 272, p. 74.
Ipsen, J. (1946). *J. Immunol.,* 54, 325.
Kayser, H. (1905). *Z. klin. Med.,* 56, 17.
Liakka, V. (1947). *Ann. Med. intern. Fenn.,* 36, 584.
McSweeney, C. J. (1952). Personal communication.
O'Regan, J. B., Heenan, M. and Murray, J. (1943). *Irish J. med. Sci.,* No. 208, p. 116.
Parish, H. J. (1949). *Proc. roy. Soc. Med.,* 42, 402.
Polano, O. (1904). *Z. Geburtsh. Gynäk.,* 53, 456.
Randall, K. J. (1949). *Proc. roy. Soc. Med.,* 42, 404.
Rolleston, J. D. (1910). *Lancet,* 2, 947.
Vahlquist, B. (1949). *Lancet,* 1, 16.

INFANTILE HYPERTROPHIC PYLORIC STENOSIS RECURRING AFTER RAMMSTEDT'S OPERATION

BY

N. K. MACRAE-GIBSON and B. L. COLES

From the Victoria Hospital for Children and the Elizabeth Garrett Anderson Hospital, London

Since the introduction of Rammstedt's operation for the treatment of infantile pyloric stenosis the mortality rate has steadily fallen; the principal cause of death is now gastro-enteritis or some other intercurrent infection. The incidence of true recurrence of symptoms also appears to be low. Tallerman (1951), Ladd, Ware and Pickett (1946), Paterson (1941), Dobbs (1941), Donovan (1937) and Bolling (1925) all reported large series with no mention of relapse. The persistence of some vomiting during the first few days after operation is common and is usually attributed to long-standing gastric distension with gastritis. This can be minimized by reducing the feeds and in severe cases by stopping all oral feeding and substituting parenteral fluids (Wood and Smellie, 1951; Grimes, Bell and Olney, 1950; Szilagyi and McGraw, 1943; Jewesbury and Page, 1937; Parsons and Barling, 1923). Faber and Davis (1940) have shown that gastric peristalsis is completely inhibited for several hours after operation and depressed for 24 hours or more. They relate this depression to post-operative distension and vomiting and claim to have greatly reduced the incidence of vomiting by withholding all oral feeds for 24 hours after operation and giving only parenteral fluids.

In this paper we present two cases in which an apparently adequate Rammstedt's operation was followed by a complete recurrence of all symptoms and signs of pyloric stenosis which failed to respond to 'eumydrin' and for which each patient required a second operation. At operation in each case a typical pyloric tumour was again found. After the second operation vomiting again persisted, and pyloric obstruction by a typical pyloric tumour was demonstrated both clinically and radiologically. Both infants eventually recovered with further medical treatment.

Case Reports

Case 1. C.E. was a normal full term boy (birth weight 7 lb. 9 oz.). He was the third child; the others were both healthy and there was no family history of pyloric stenosis. He was fully breast fed, and began to vomit when 2 weeks old. He failed to respond to out-patient treatment with 'eumydrin' and was admitted to hospital aged 19 days. On examination, projectile vomiting, visible peristalsis and a palpable pyloric tumour were present. When aged 22 days a Rammstedt's operation was performed under general anaesthesia and a large pyloric tumour divided. Small vomits persisted after operation but were controlled with 0·6% alcoholic 'eumydrin', minims 1, before all eight feeds. He was discharged 35 days after operation. Vomiting began again immediately and he was admitted again after a further week. A barium meal showed spasm of the pylorus, only half the meal having left the stomach after one hour. Three days later, aged 67 days and 45 days after the first operation, a second operation was performed under general anaesthesia. Adhesions were present between the intestines, liver and peritoneum, but these were not causing obstruction, and a typical pyloric tumour was again present. The previous incision was replaced by a fibrous scar. The tumour was redivided, and the duodenum was opened at one point and satisfactorily closed. Slight post-operative vomiting occurred but the infant's general condition remained good and he gained weight. The vomiting became severe and projectile during the second week after operation and did not respond to gastric wash-outs and glyceryl trinitrite, grain $\frac{1}{100}$, daily. Two weeks after the second operation, aged 82 days, he was transferred to the Victoria Hospital for Children. His weight was then 7 lb. 9¾ oz. On examination, he was dehydrated with visible peristalsis and a palpable pyloric tumour. A further barium meal (two months after the first operation, and two weeks after the second operation) showed typical pyloric stenosis (Fig. 1). After rehydration with subcutaneous salines, 'eumydrin', minims 2, eight times daily, was started and the vomiting responded well. The dose was gradually reduced and discontinued after five weeks. He was discharged seven weeks after admission, weighing 10 lb. 11½ oz., free from symptoms and on full feeds.

Case 2. S.W., a boy of birth weight 6 lb. 6 oz., was born three weeks prematurely. The mother was Rh negative, the child Rh positive but there was no evidence of erythroblastosis. He was the second child, the other was well, and there was no family history of pyloric stenosis. He was breast fed for five weeks when he began vomiting, and breast feeding was discontinued. He was

tried on three different dried milks but the vomiting increased. All feeds had been vomited for 10 days before

Fig. 1.—Two months after the first operation and two weeks after the second operation showing after a barium meal typical pyloric stenosis.

admission and the vomiting was projectile in character. He had been constipated for several days before admission. On examination, he was slightly dehydrated with visible peristalsis and a palpable tumour. 'Eumydrin', minims 5 and 6 before alternate feeds (five feeds daily), was tried for five days without success. The next day (aged 9 weeks) Rammstedt's operation was performed under local anaesthesia, and a typical tumour was found. Vomiting continued after operation with gastric residues of 3 to 6 oz. daily. Four days after operation 'eumydrin' was restarted and increased to 4 minims before feeds without effect. Twelve days after the first operation a second Rammstedt's operation was performed under general anaesthesia and a pyloric tumour was again found. This was redivided. The infant's postoperative condition was poor with haematemesis and melaena requiring intravenous fluids and blood transfusion. He also developed some sepsis in the wound which responded to penicillin and streptomycin. Oral feeding was begun four days after operation. On the tenth day after the second operation vomiting again began with gastric residues of 2 to 4½ oz. daily. Radiographs showed persistence of pyloric obstruction on

screening. 'Eumydrin' was tried again and the dosage increased to 8 minims before all five feeds. The vomiting gradually decreased, the gastric residues fell to 1½-2 oz. daily, and he slowly gained weight. Fourteen and a half weeks from the second operation a barium meal still showed total obstruction at the pylorus up to 10 minutes after the meal (Fig. 2). Unfortunately no further films were taken. The child was then discharged (aged 5 months) on 'eumydrin', minims 8 before meals, with only occasional vomiting, and weighing 11 lb. 2½ oz. His subsequent progress was uneventful apart from acute otitis media at the age of 8 months. When aged 11 months a further barium meal showed normal emptying of the stomach. The 'eumydrin' was stopped over the next two weeks with no return of vomiting and he has remained well.

Discussion

Aird (1949) believes that continued vomiting after Rammstedt's operation suggests incomplete division of the tumour and most authorities are in agreement. References to incomplete division found at necropsy or at second operations are made by Ward-McQuaid and Porritt (1950) who reported one case where incomplete section was found at necropsy. They considered re-operation in a second case but the child responded to medical treatment. Grimes et al. (1950) cite one case of recurrence, the second operation being performed through a different area. Frazier and Warfield (1949) consider that inadequate division was the cause of continued vomiting in their case, which was re-operated on six weeks after the

Fig. 2.—Film taken 10 minutes after a barium meal showing total obstruction 14½ weeks after second operation.

first operation and again found to have a typical tumour. Schaefer and Erbes (1948) mention five cases requiring re-operation. All recurrences were thought to be due to inadequate surgery. Jacoby (1944) reports a case where vomiting persisted after operation, but no further surgery was undertaken because of the infant's poor general condition. The child subsequently died but there is no mention of the state of the pylorus at necropsy. Szilagyi and McGraw (1943) in an extensive paper suggest that failures after operation were due to incomplete section of the muscular fibres although the gross anatomy appeared adequate at the time of operation. They also suggest that some nervous pathway as yet unidentified may play a part in the causation of pyloric stenosis, and that failure to divide these may be the cause of some recurrences. They give the incidence of recurrence as approximately 2% after correction has been made for cases of mistaken diagnosis, but from the cases reviewed in this paper the incidence appears to be nearer 0·3%. They report one case of their own which responded to a second operation. Jewesbury and Page (1937) had two recurrences in their series. One had a further operation but died, the other infant died without a second operation. Thompson and Gaisford (1935) also thought recurrences due to inadequate surgery but reported no cases of their own. Lanman and Mahoney (1933) had two cases requiring further surgery. In both cases at re-operation the tumour was found to have been incompletely divided. Gaisford (1931) and Still (1923) each reported one case of relapse after operation. In Gaisford's case, re-operation took place 26 days after the first operation, and a second tumour was found proximal to the original one. He considered that fibres at the gastric end of the first tumour were not completely sectioned, and attributed the relapse to this.

Another possible cause of recurrence of symptoms after operation is the formation of adhesions resulting in obstruction. Donovan (1946) reported a case in which the symptoms were relieved after division of adhesions. Rinvik (1940) reported two cases of relapse. One recovered after a second Rammstedt's operation but the second patient continued to vomit, and at a third operation adhesions were thought to be the cause. Miller (1946) treated a case of relapse by gastro-enterostomy but gave no definite cause for the continuation of symptoms. A duodenal membrane or some similar abnormality was suspected. The only case in which a true recurrence of the tumour was suggested was in that reported by Rosenblum (1950). A typical small tumour was found at the first operation and the infant progressed satisfactorily for two weeks. He

then developed eczema and gastro-enteritis and started to vomit. The vomiting continued and 69 days after operation a barium meal showed signs of pyloric stenosis. A further operation was performed three days later and the site of the previous operation could not be identified. Although Rosenblum agrees that relapses are usually due to inadequate surgery, he believed this case to be one of true recurrence because of the length of time between the two operations, the symptoms having completely abated for a time and the child having gained 72 oz. Severe vomiting ceased after the second operation but there were still occasional attacks of vomiting and eczema which were thought to be due to food allergy. Frazier and Warfield also mentioned the connexion of allergy with pyloric stenosis, as a child reported by them only ceased vomiting completely after the second operation when a special diet and sedatives were given. There was no suggestion of allergy and no family history of it in either of our cases.

In both our cases, the second operation was performed with particular care and the macroscopic appearances were entirely satisfactory. We feel it unlikely that inadequate section could have been responsible for the continued symptoms after the second operation. Both tumours had recurred at the original site in contrast to Gaisford's case where the second tumour was proximal to the first. This excludes the possibility of incomplete division at the gastric end of the tumour which appears to be a common site in which a few fibres may escape section. In Gaisford's case 12 days elapsed after operation before the recurrence of symptoms. Other authors who consider their relapses due to inadequate surgery report the onset of vomiting any time from immediately after operation to 12 days post-operatively. In case 1 the exact time of recurrence of vomiting was rather masked by 'eumydrin' after the first operation but was definite at one month. Vomiting began again one week after the second operation. Case 2 continued to vomit after the first operation and vomiting began again 10 days after the second. While these times of remission are short, we do not feel that they necessarily prove that regeneration was taking place from fibres which were not completely divided. Post-mortem material suggests that after a clinically successful operation the gap between the fibres closes in two to three weeks (Wollstein, 1922). The tumour is then softer than at first and disappears completely after one to two months. This contrasts with the persistence of the tumour into adult life after gastro-enterostomy (Donovan, 1946; Holt, 1917). In our cases, the gap was found to be closed at the second operation at

45
how
ance
of th
con
atter
two
tend

T
diffe
ently
radi
mon
Run
of c
relap
are
men
the
appe
Fig.
mon

W

FIG. 3
opera

45 days and 12 days respectively. The tumours, however, were hard and presented a typical appearance as at the first operation. Normally the cut ends of the muscle are separated by a thin layer of fibrous connective tissue as healing proceeds and there is no attempt at proliferation. As an explanation for two relapses in our cases, we postulate an abnormal tendency of the pyloric fibres to proliferate.

The x-ray appearances are not a great help in the differential diagnosis of relapse, as after an apparently successful Rammstedt's operation abnormal radiological appearances may persist for some months (Olnick and Weens, 1949; Andresen, 1940; Runström, 1939). There seems no radiological means of distinguishing between a true recurrence or a relapse due to inadequate surgery, though x-rays are of use in excluding such conditions as duodenal membrane if vomiting persists after operation. That the pylorus in some cases shows normal x-ray appearances shortly after operation is shown in Fig. 3. This infant had a Rammstedt's operation two months before the radiograph was taken.

Whatever the cause of recurrence after operation the prognosis seems poor. If typical signs and symptoms recur after Rammstedt's operation the treatment of choice would appear to be a short trial of medical treatment with early operation if this does not produce a remission. A re-operation should not be deferred until the general condition has deteriorated. It is possible that a modification of the classical Rammstedt's operation might be more successful in cases of relapse. Grimes *et al.* (1950) reported less post-operation regurgitation in cases where an elliptical wedge of tissue was removed for histological section and this procedure might be worthy of trial in selected cases. The disadvantage of this operation is the increased risk of haemorrhage and formation of adhesions. If the second operation is unsuccessful prolonged medical treatment with an adequate dosage of 'eumydrin' and gastric lavage should be tried.

Summary

Two cases of pyloric stenosis recurring after Rammstedt's operation are reported. In each case a further recurrence occurred after a second operation. Both cases eventually responded to medical treatment.

The literature is reviewed and the likely causes of relapse are discussed.

It is suggested that true recurrences may be due to an abnormal tendency of the pyloric fibres to proliferate.

FIG. 3.—Radiograph taken two months after a successful Rammstedt's operation. The pyloric antrum, the pylorus and the first part of the duodenum are outlined with barium and air.

REFERENCES

Aird, Ian (1949). *A Companion in Surgical Studies*, p. 569. Edinburgh.
Andresen, K. (1940). *Acta paediat., Uppsala*, 27, 334.
Bolling, R. W. (1925). *J. Amer. med. Ass.*, 85, 20.
Dobbs, R. (1941). *Proc. roy. Soc. Med.*, 35, 51.
Donovan, E. J. (Ladd, W. E. and Strauss, A. A.) in discussion, Ladd, p. 560, Strauss, p. 561 (1937). *J. Amer. med. Ass.*, 109, 558.
—— (1946). *Ann. Surg.*, 124, 708.
Faber, H. K. and Davis, J. H. (1940). *J. Amer. med. Ass.*, 114, 847.
Frazier, C. A. and Warfield, J. O. (1949). *W. Va. med. J.*, 45, 235.
Gaisford, W. (1931). *Archives of Disease in Childhood*, 6, 111.
Grimes, O. F., Bell, H. G. and Olney, M. B. (1950). *J. Pediat.*, 37, 522.
Holt, L. E. (1917). *J. Amer. med. Ass.*, 68, 1517.
Jacoby, N. M. (1944). *Lancet*, 2, 748.
Jewesbury, R. C. and Page, C. M. (1937). *St. Thom. Hosp. Rep.*, 2nd ser., 2, 141.
Ladd, W. E., Ware, P. F. and Pickett, L. K. (1946). *J. Amer. med. Ass.*, 131, 647.
Lanman, T. H. and Mahoney, P. J. (1933). *Surg. Gynec. Obstet.*, 56, 205.
Olnick, H. M. and Weens, H. S. (1949). *J. Pediat.*, 34, 720.
Parsons, L. G. and Barling, S. G. (1923). *Lancet*, 1, 59.
Paterson, D. (1941). *Proc. roy. Soc. Med.*, 35, 49.
Rinvik, R. (1940). *Acta paediat., Uppsala*, 27, 295.
Rosenblum, A. H. (1950). *Amer. J. Dis. Child.*, 80, 356.
Runström, G. (1939). *Acta paediat., Uppsala*, 26, 383.
Schaefer, A. A. and Erbes, J. (1948). *Surg. Gynec. Obstet.*, 86, 45.
Still, G. F. (1923). *Brit. med. J.*, 1, 579.
Szilagyi, D. E. and McGraw, A. B. (1943). *Surgery*, 13, 764.
Tallerman, K. H. (1951). *Proc. roy. Soc. Med.*, 44, 1055.
Thompson, W. A. and Gaisford, W. F. (1935). *Brit. med. J.*, 2, 1037.
Ward-McQuaid, J. N. and Porritt, B. E. (1950). *Lancet*, 1, 201.
Wollstein, M. (1922). *Amer. J. Dis. Child.*, 23, 511.
Wood, E. C. and Smellie, J. M. (1951). *Lancet* ,2, 3.

BLOOD GLUCOSE CHANGES IN THE NEWBORN

1. THE BLOOD GLUCOSE PATTERN OF NORMAL INFANTS IN THE FIRST 12 HOURS OF LIFE

BY

R. D. G. CREERY and T. J. PARKINSON

From the University Department of Child Health and the Department of Pathology, Southmead Hospital, Bristol

Many investigations of the blood sugar levels of newborn infants have been made. The literature has been reviewed by Norval, Kennedy and Berkson (1949), who concluded that the values found varied widely. They considered this to be due to several factors, including the method of determination used, the source of the blood sample and the age of the infants.

Previous investigators have tended to estimate the blood sugar levels at birth, and subsequently at varying intervals throughout the first days and weeks of life. For example, Ketteringham and Austin (1938), using the modified Folin-Malmros method, made estimations at birth, at 3 to 6 hours and thereafter daily for the first three days of life. Hanley and Horn (1943) used the Jeghers-Myers modification of the Folin-Malmros method and made estimations at birth, at 1 hour and at 6 hours.

Both Ketteringham and Austin and Hanley and Horn have included in their results many infants, far from normal, who had been delivered by forceps or by other complicated manoeuvre, and often under ether anaesthesia which is known to raise the blood sugar level in the infant significantly.

It is evident that little is known concerning the detailed behaviour of the blood glucose levels of normal infants during the first critical hours when adaptation to a completely changed environment is taking place.

The purpose of the present investigation was to obtain a series of levels during the first 12 hours of life in full-term infants born of healthy mothers, uninfluenced by drugs known to affect the blood sugar, delivered spontaneously by the vertex, and themselves showing no abnormal features during the neonatal period.

These results will be used as a base line of normality in our subsequent investigations of the blood sugar levels of abnormal infants, whether asphyxi-ated, shocked or suffering from cerebral damage, or any other form of 'birth injury'.

Material

The subjects of this study were babies born at Southmead Hospital during the years 1950 and 1951. The primary selection was random, all babies born at an hour convenient to the clinical observer and to the laboratory staff being included. From this series, normal babies were selected by conformity to the following criteria: (1) mother unanaesthetized, but having in most cases received routine doses of analgesics; (2) spontaneous vertex delivery at full term; (3) no signs of asphyxia in the baby, regular respiration being established within three minutes of birth in all cases; (4) no observed abnormality of temperature, pulse rate, or respiration; (5) no signs suggesting cerebral damage, neither tense fontanelle, muscular twitchings, shrill cry nor abnormal muscle tone; (6) no clinical abnormality developing before discharge from hospital which could be attributed to birth trauma. (It was considered unnecessary to make a late follow-up study of these babies.)

Included in the series is one pair of twins (babies C6 and C7).

The analgesic routine included any of the following, depending on the duration of labour: (1) self-administered nitrous oxide and air from a Minnitt's machine; (2) pethidine hydrochloride in doses of 100 mg. by mouth, or by intramuscular injection, repeated in cases of prolonged labour; (3) a mixture, containing chloral hydr., gr. 20, pot. brom., gr. 20, nepenthe, minims 20, which might be repeated in prolonged labours.

Of these drugs, Larson (1949) has shown that morphia, the active principle of nepenthe, and pethidine ('meperidine'), are without effect on the blood glucose concentration in doses of the size of those used, and a search of the literature gives no

reason to attribute such an effect to chloral, bromide or nitrous oxide.

Method

The method used to estimate the blood glucose concentration was that of King and Garner (1947). An extensive experimental review of this method has been made in order to assess its range of error. The results of this investigation of its accuracy and consistency at the low concentration found in neonates are being published elsewhere by C. N. Chapman. The method is quick, and convenient and reasonable delay in analysis does not affect its accuracy. Only 0·05 ml. of blood is used and as frequent estimations were to be made this provided accuracy with small blood loss to the baby, an important point when nine samples had to be secured. In the preliminary investigation it was found that 95% of results were consistent to within 5 mg. per 100 ml., when the same sample of blood was subject to repeated analysis, and with this knowledge it was decided to omit duplicate sampling and analysis within the series.

The first sample was taken from the ear of the mother at the moment of crowning of the foetal head, or as near thereto as possible. The next sample was taken from the umbilical vein by the method of Hanley and Horn (1943). This was placed in a bottle containing the standard oxalate-fluoride blood sugar anticoagulant (Harrison, 1947); and a mixed sample withdrawn for analysis. Such samples are strictly comparable with the directly drawn capillary samples. Similar specimens were obtained from the umbilical artery in a number of cases. All subsequent samples were secured from a puncture of the ether-cleaned heel of the infant.

As delivery was thought likely to upset the pre-existing foetal equilibrium, it was decided to follow the variations of blood glucose at half-hour intervals for the first three hours of life. It was considered that any noteworthy change occurring later would be detected by investigations at three-hourly intervals.

On each occasion when a sample was taken the infant was assessed clinically, particular attention being paid to the temperature, pulse rate, respiration, muscle tone, muscle twitching or its absence, the tension of the fontanelle and the type of cry.

No fluid or feed was given to any infant during its first three hours of life, and subsequently, if any was given, it immediately followed the taking of a sample and was thus unable to influence the next sample, taken three hours later.

Results

The results of a study of 23 male babies are shown in Table 1. The value for the mother's blood glucose at the moment of delivery was not investigated at the beginning of the study, nor was that for the umbilical artery. Later, occasional lapses occurred when blood could not be taken at the exact time required, or a mishap occurred to the specimen. All the values estimated are recorded in Table 1.

The scatter of individual values about the mean is wide, from 49-118 mg. per 100 ml. in the umbilical artery, the most scattered, but even at two hours, where scatter is least, varying from 30 to 76 mg. per 100 ml., and the histograms (Fig. 1) show this. In view of the small numbers involved they correspond reasonably well with the normal distribution which Wooton, King, Maclean Smith and Haslam (1951) found random fasting adult blood glucose values to follow.

The mean values show a steady decline from the mother, 115·1 mg. per 100 ml., through the arterial side of the foetal circulation represented by the umbilical vein, 83·7 mg., to the venous side represented by the umbilical artery, 74·0 mg. per 100 ml. Once independent, not even this level is maintained by the baby, for by half an hour after birth a fall to 66·7 has occurred, and, by an hour, to 55·5 mg. per 100 ml. The mean values do not subsequently differ markedly from this.

A study of the histograms suggests that the results show less scatter as the baby gets older. Calculation gives the Spearman rank order coefficient of correlation between the standard deviation of each age series from its mean with the age of the babies in the series as −0·48, which indicates that there is a definite but not complete inverse correlation, and that the scatter of values is less as the babies grow older.

Table 2 and Fig. 2 give the results of a parallel study of 23 female babies. In this series, the mean blood glucose of the mothers is lower, 100·3 mg. per 100 ml., and this is true also of the blood in the umbilical vessels (75·7 and 60·5 mg. per 100 ml.). Stability appears to be reached earlier at half-an-hour, although this may only be because the maternal level was nearer to that at which the baby aims, and in any case is never so complete as in the male babies, the means varying from 46·5 to 58·0 mg. per 100 ml. as against 51·7 to 55·5 for the males, after the first hour.

Fig. 2 shows that although the means are more variable, the scatter around them is smaller than it was with the male babies, and the standard deviations, whose mean after the first hour is 11·4 as against 12·9 for the males, measure this. The coefficient of correlation for standard deviation with age is −0·92, almost perfect inverse correlation.

In adult life the blood glucose content does not appear to be influenced by the sex of the individual, and the results of this study show that this is true also of newborn babies. Table 3 is a consolidation of the two series into a larger series with 46 infants in each age group.

TABLE 1

BLOOD GLUCOSE OF NORMAL MALE BABIES

No.	Mother	Artery	Vein	½	1	1½	2	2½	3	6	9	12
C1	—	—	80	77	—	62	60	—	30	43	32	25
C3	—	—	65	49	35	35	46	46	43	60	30	10
C10	—	—	82	69	52	42	44	48	50	53	49	63
C14	—	—	90	56	51	51	51	51	48	49	49	57
C15	—	—	120	73	56	52	36	46	36	50	64	50
106	111	84	84	76	70	64	59	52	54	62	46	52
111	111	90	95	87	73	62	45	43	34	61	45	54
113	—	49	57	45	45	45	38	56	40	39	49	46
114	115	—	—	65	50	46	49	62	60	60	65	59
123	103	64	76	69	52	44	49	57	67	44	44	38
124	122	—	—	94	87	53	53	62	62	60	62	46
201	123	—	93	92	79	65	53	54	54	49	65	66
202	—	118	126	110	82	79	52	42	34	44	53	46
204	108	—	68	62	49	42	49	44	46	44	57	60
205	129	86	86	49	32	24	32	41	39	46	39	45
209	146	77	91	65	54	57	61	64	65	54	57	57
211	100	—	68	49	49	65	69	75	75	76	54	75
213	120	52	82	52	35	35	30	43	49	54	54	65
215	—	54	68	60	49	60	76	90	90	82	60	62
219	136	87	91	56	54	47	49	35	45	49	44	44
220	87	62	77	44	42	42	57	64	64	62	62	67
226	102	65	76	57	57	60	60	60	60	57	60	52
301	114	—	—	79	68	65	70	75	75	69	57	54
Mean	115·1	74·0	83·7	66·7	55·5	52·0	51·7	55·0	53·0	55·1	52·0	51·9
S.D.	15·1	20·1	17·0	17·5	15·0	12·9	11·8	13·3	15·4	10·7	10·2	14·1

FIG. 1.—Histograms of blood glucose of male babies and their mothers. Vertical scale number in group, horizontal scales mid-group blood glucose.

TABLE 2

BLOOD GLUCOSE OF NORMAL FEMALE BABIES

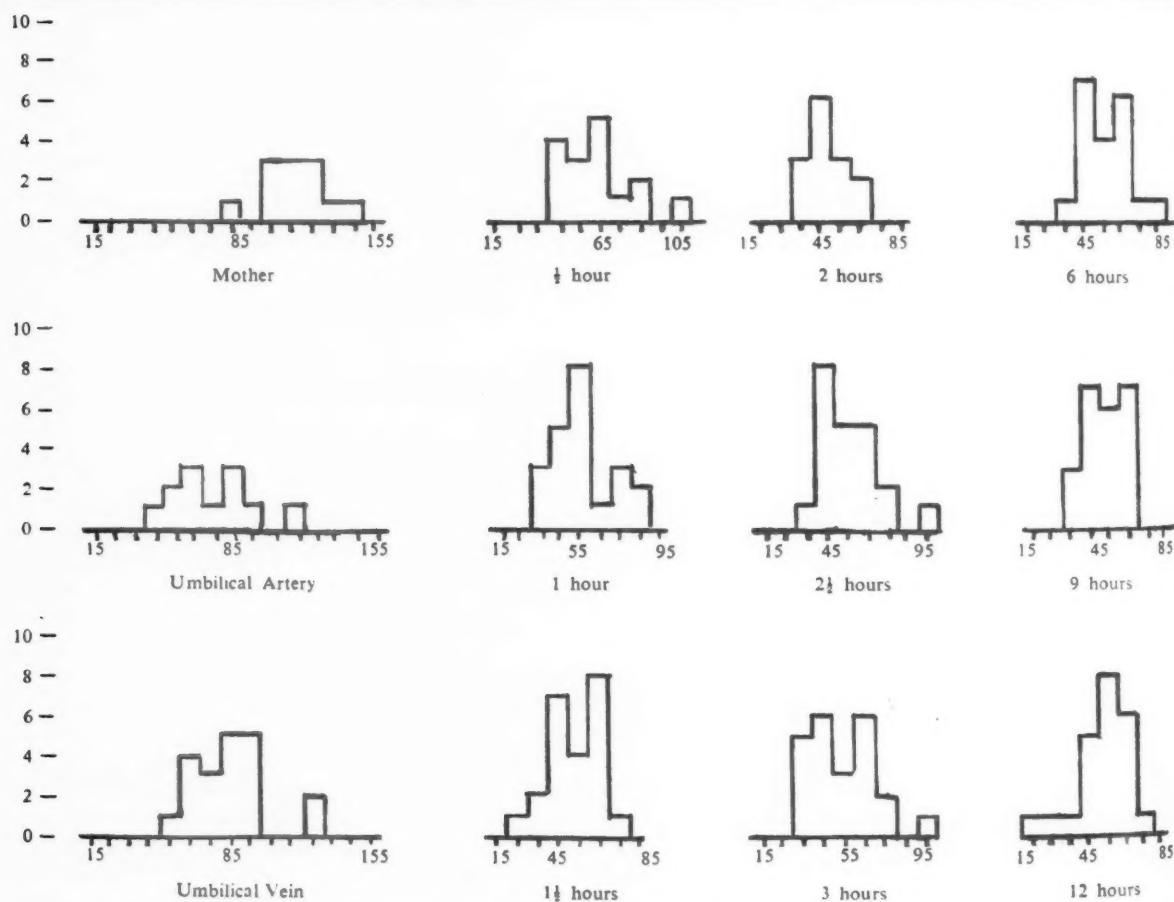| No.	Mother	Artery	Vein	½	1	1½	2	2½	3	6	9	12
C6	—	—	70	52	50	46	57	56	55	62	59	52
C7	—	—	80	48	41	68	70	63	66	65	52	48
C8	—	—	83	40	21	21	35	55	64	65	73	75
C12	—	—	103	69	69	69	77	77	85	65	64	67
C13	—	—	90	62	37	29	37	37	37	32	36	34
102	95	—	69	35	35	42	46	68	70	48	48	48
103	68	40	52	68	72	62	48	46	52	48	46	41
104	—	—	54	27	44	49	50	46	46	46	46	46
107	106	—	82	64	52	46	52	54	68	62	43	60
112	95	—	79	46	38	45	49	44	45	62	37	47
115	90	—	—	49	38	49	38	72	65	60	56	52
116	76	47	49	48	46	49	54	56	57	52	44	44
119	104	57	76	46	37	49	53	53	54	45	61	52
120	106	49	57	70	49	52	54	62	61	54	54	52
126	75	—	70	54	61	61	65	65	65	46	40	54
127	127	54	87	44	32	32	52	52	54	70	52	40
128	81	57	61	49	52	46	34	34	34	40	49	49
203	—	70	84	60	42	50	57	54	56	53	44	45
206	100	70	76	47	24	19	38	46	52	57	57	60
210	118	—	91	84	70	74	68	74	62	64	50	54
221	114	—	92	68	60	60	60	60	60	65	65	57
223	154	107	107	68	54	54	70	61	62	57	54	60
225	95	54	54	46	46	54	60	65	65	70	57	46
Mean	100·3	60·5	75·7	54·1	46·5	48·9	53·2	56·5	58·0	56·0	51·6	51·8
S.D.	19·8	18·8	16·5	13·1	13·7	14·3	12·2	11·3	11·3	10·0	9·3	9·1
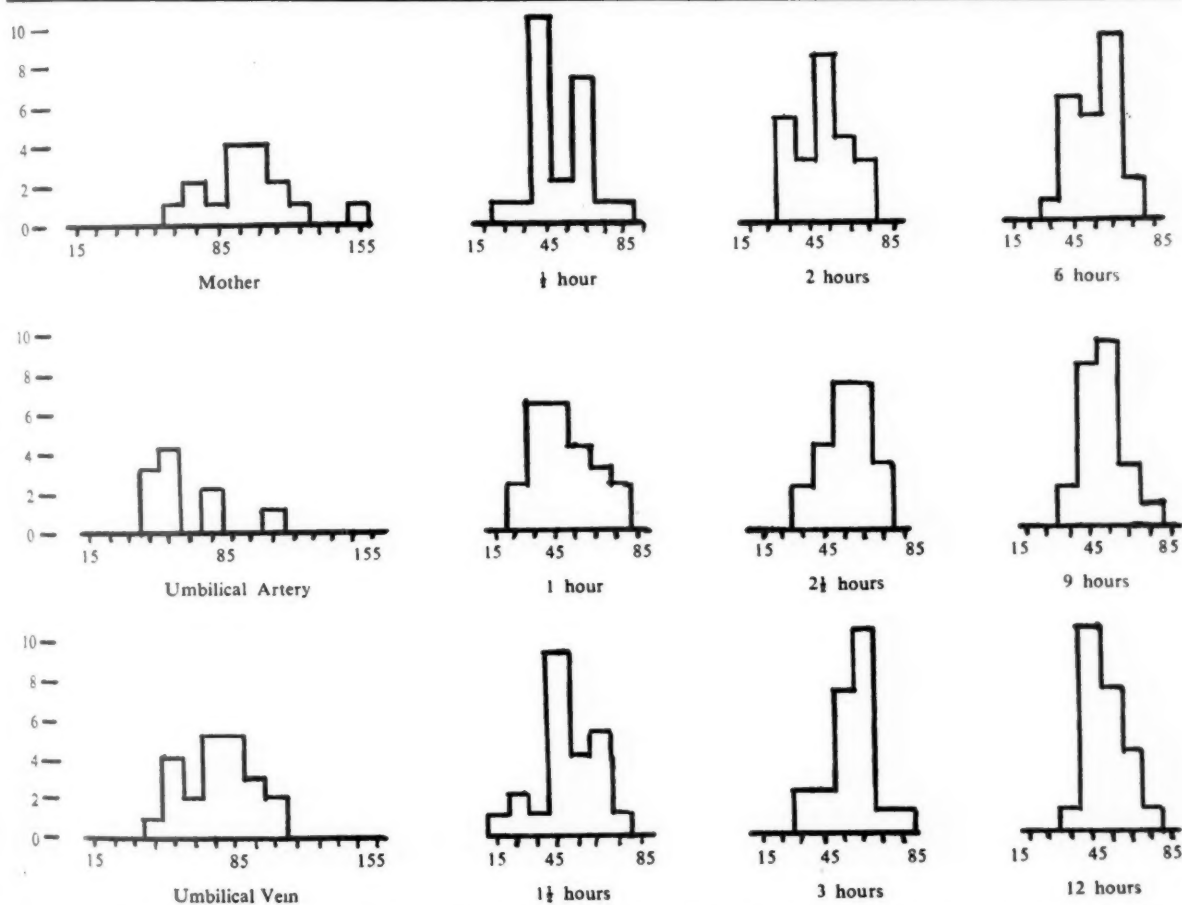
FIG. 2.—Histograms of blood glucose of female babies and their mothers.   Vertical scale number in group, horizontal scales mid-group blood glucose.

TABLE 3

MEANS AND STANDARD DEVIATIONS IN TWO SERIES

	Means			Standard Deviations		
	Male Babies	Female Babies	All Babies	Male Babies	Female Babies	All Babies
M	115·1	100·3	107·5	15·2	19·8	23·1
A	74·0	60·5	67·9	20·1	18·8	20·1
V	83·7	75·7	79·6	17·0	16·5	16·7
½	66·7	54·1	60·4	17·5	13·1	16·6
1	55·5	46·5	50·7	15·0	13·7	15·8
1½	52·0	48·9	50·5	12·9	14·3	13·4
2	51·7	53·2	52·4	11·8	12·2	12·1
2½	55·0	56·5	55·8	13·3	11·3	12·0
3	53·0	58·0	55·5	15·4	11·3	13·6
6	55·1	56·0	55·5	10·7	10·0	10·6
9	52·0	51·6	51·8	10·2	9·3	9·7
12	51·9	51·8	51·8	14·1	9·1	12·0

No distinct pattern is apparent in the serial values for each baby after the initial fall from the maternal level has occurred. Some babies have an almost constant blood glucose level (e.g. C14, 104); others fluctuate widely (102, 215). With this in mind it was thought that a mean value for the relatively stable period from three to 12 hours was a more suitable basis for comparison with the birth weight of the baby than the single values used by previous workers. These data, birth weight and mean blood glucose values, are given in Table 4. The weights range from 2·6 kg. to 4·5 kg. and the mean glucose concentrations from 32 to 73 mg. per 100 ml. These results are presented diagrammatically in Fig. 3, which shows clearly that there is no correlation between them.

TABLE 4

BIRTH WEIGHT AND MEAN BLOOD GLUCOSE VALUE IN TWO SERIES

Male Babies	Mean Glucose	Weight (100 g.)	Female Babies	Mean Glucose	Weight (100 g.)
C1	32	31	C6	57	28
C3	36	36	C7	58	31
C10	54	29	C8	69	31
C14	51	42	C12	70	32
C15	50	31	C13	35	34
106	53	34	102	53	33
111	49	37	103	47	28
113	43	33	104	46	34
114	61	34	107	58	36
123	48	33	112	48	38
124	57	28	115	58	29
201	58	26	116	49	26
202	44	31	119	53	44
204	52	26	120	55	31
205	42	33	126	51	34
209	58	35	127	54	37
211	70	37	128	44	32
213	54	30	203	50	31
215	73	29	206	56	29
219	45	28	210	57	36
220	64	30	221	62	41
226	57	30	223	58	45
301	64	33	225	59	36

Discussion

In all the cases we have studied we have found the blood of the umbilical vein to contain less glucose than the mother's blood taken at almost the same
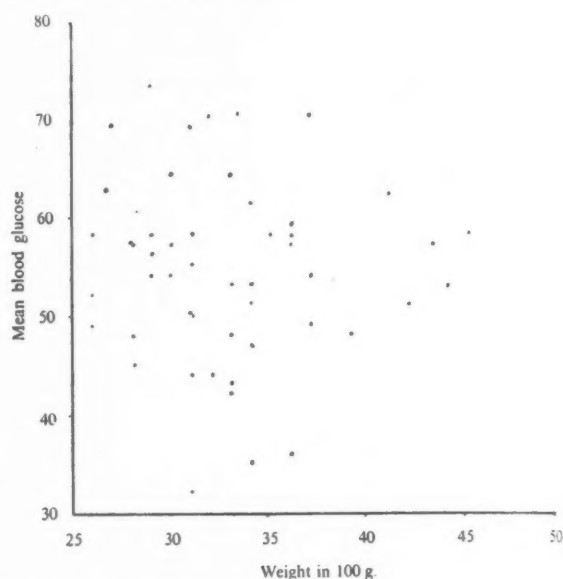
FIG. 3.—Scatter diagram showing birth weight and mean of blood glucose at 3, 6, 9 and 12 hours after birth.

time, and this can be assumed to be true of late foetal life also. This confirms the work of Morriss (1917), Ketteringham and Austin (1938) and Hanley and Horn (1943).

In the values recorded for the umbilical artery the only surprising feature is that in five cases it has equalled that of its accompanying vein (cases 106, 205, 116, 223 and 225), at least within experimental limits. Hanley and Horn also report this in eight of their cases. It appears probable that on all these occasions blood was actually taken from the wrong vessel, an error by no means improbable, for there is considerable difficulty in taking blood from a contracted and pulseless artery in an often oedematous cord.

The apparent stabilization which we found to be progressive throughout the period studied is in accord with the results of McKittrick (1940), who reported increasing stability during the whole of the two-week period of his investigation. Norval, Kennedy and Berkson (1949) on the contrary, found no evidence of stabilization during the first week.

Greenwald and Pennel (1930) reported that the weights of the infants they studied bore no relationship to the infants' blood sugars, and Hanley and Horn (1943), give similar results. The results presented confirm this conclusion, and by having taken a mean blood glucose level as a basis for correlation, the effect of the fluctuation of the baby's blood glucose with the passage of time has been minimized. It had been thought that the failure of earlier workers

to recognize and allow for this fluctuation might account for their inability to detect any correlation of blood glucose with birth weight. This proved not to be the case.

The main result of this study, is however, to provide a background against which future blood glucose estimations can be considered. In the past the terms hypoglycaemic and hyperglycaemic have been applied to newborn babies whose blood glucose level was within the range of twice the standard deviation, either side of the mean, a range which includes 95% of the results of a normal distribution. In numerical terms we would suggest that all values between 30 and 75 mg. per 100 ml. are quite likely to be found in normal babies if the blood glucose is estimated by the method we have used, and the baby is between 1 and 12 hours old. Within the first hour, the baby's blood glucose is largely dependent on the widely variable blood glucose of its mother, and this might contain in itself important considerations from a clinical point of view.

Our object in this work was to determine a basis for extended studies of the clinical and biochemical indices of birth injury, and we realize that our strict criteria of normality restrict this basis to a limited number of babies and one type of delivery. It is proposed to publish shortly results relating to certain other types of delivery and later to 'injured' babies, where 'injured' will be interpreted in the widest sense. Work is also in progress to establish the mechanisms by which the physiological adjustments to birth are controlled.

Summary

Previous work on the blood glucose level of newborn babies is reviewed briefly, and the absence of intensive serial study noted.

Results are presented to show the changes which took place in 46 normal babies, born spontaneously to normal, unanaesthetized mothers.

It was found that during the first hour after delivery, the babies' blood glucose fell from 79 mg. per 100 ml., as found in the umbilical vein, to a mean value of 52 mg. per 100 ml., and that this level was maintained with varying constancy by individual babies.

From a total of 356 estimations it is concluded that the normal blood glucose range for babies between 1 and 12 hours old is 30 to 75 mg. per 100 ml.

This range appears to narrow slightly but progressively during this period.

There is no difference in blood glucose between male and female babies.

There is no relationship between the birth weight of these full term babies and the mean of its blood glucose at 3, 6, 9 and 12 hours.

REFERENCES

Greenwald, H. M. and Pennell, S. (1930). *Amer. J. Dis. Child.*, **39**, 281.
Hanley, B. J. and Horn, P. (1943). *Amer. J. Obstet. Gynec.*, **46**, 502.
Harrison, G. A. (1947). *Chemical Methods in Clinical Medicine*, 3rd ed. London.
Ketteringham, R. C. and Austin, B. R. (1938). *Amer. J. med. Sci.*, **195**, 318.
—— and Garner, R. J. (1947). *J. clin. Path.*, **1**, 30.
Larson, E. (1949). *Endocrinology*, **44**, 301.
McKittrick, J. B. (1940). *J. Pediat.*, **16**, 151.
Morriss, W. H. (1917). *Bull. Johns Hopk. Hosp.*, **28**, 140.
Norval, M., Kennedy, R. L. J. and Berkson, J. (1949). *J. Pediat.*, **34**, 342.
Wooton, I. D. D., King, E. J., Maclean Smith, I., and Haslam, Ruth M. (1951). *Biochem. J.*, **48**, Proc. 59.

A COMPARATIVE STUDY OF THE CIRCULATING EOSINOPHIL LEVEL IN BABIES

PART II: IN FULL TERM INFANTS

BY

JOAN M. BURRELL
From the Department of Child Health, University of Aberdeen

This study of circulating eosinophils in full term infants was undertaken for comparison with the group of premature infants originally investigated (Burrell, 1952). As it was desirable to follow up some normal babies for a period similar to the average length of stay of the premature babies in the special nursery, some mothers of full term babies were asked to permit weekly or twice-weekly visits to the home for blood samples to be taken there. The reasons were explained to the mother in hospital and she was shown exactly what was done. Full cooperation was obtained from all the mothers approached. Ninety-three full term babies were studied in hospital until discharge on the seventh or eighth day. All were healthy babies, born spontaneously after a normal labour, the birth weight varying from 5 lb. 10 oz. to 9 lb. 14 oz. Of these, 25 were then followed up by visits to the home until the age of 12 weeks. These 25 babies were selected only because their homes were in one of two areas, (1) near the hospital, (2) near my own home. These two areas were chosen to make the collection of specimens as little time-consuming as possible. The follow-up period was fixed at 12 weeks though there would have been no difficulty had a more prolonged period been decided upon.

Samples of blood were collected at approximately the same time for each child and the time of the visit was arranged with the mother to suit her convenience. Blood was withdrawn before a feed.

Technique

The methods of withdrawing blood samples, mixing, staining and counting were identical with those described in Part I.

Results

Nine hundred and seventy-one counts were made altogether including 321 counts done on the 25 babies during the 12-week follow-up period.

Counts made on the first day of life for all full term babies showed that many of them have some eosinophils circulating at the time of delivery but the figure is very low and gives only 0.01% to 0.04% when calculated on the white cell count. This is in direct contrast to the complete absence of eosinophils from the peripheral circulation of the premature baby. The rate of increase is more rapid and by the end of the first week most full term babies have a higher absolute count than premature babies of the same age, but this increased rate of production is not maintained after the end of the second week of life when most full term babies have reached a stable level of circulating eosinophils.

The range of eosinophils for the present group of infants was as follows:

1st day (93 infants)	..	0 to 264 per c.mm. (average count 52·4)
84th day (25 infants)	..	143 to 700 per c.mm. (average count 421·6)

Average curves have been plotted for the daily counts in the first week and then weekly up to the age of 7 weeks for both full term and premature babies. These two graphs are compared in Fig. 1 which
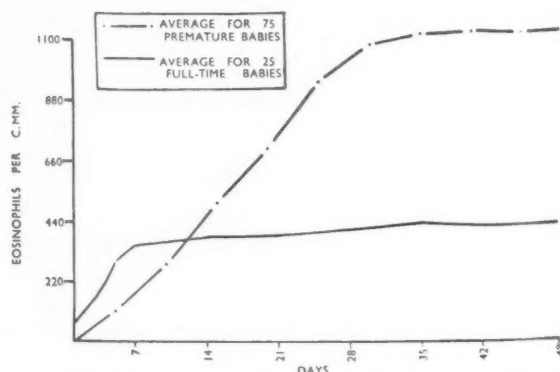

FIG. 1.—Graph of eosinophil rise for full-term and premature babies.

shows the slow rise and high stable level attained by the premature babies and the more rapid rise and moderate level of the full term babies. Comparison of actual figures is interesting, and Tables 1, 2, 3 and 4 show counts for 10 infants in each of three weight

No. 10.—This child had an upper respiratory infection of moderate severity with associated otitis media with purulent discharge. During this period there was depression of the eosinophils. Following treatment, the condition cleared quickly with a rise of eosinophils to previous levels.

TABLE 1
ABSOLUTE EOSINOPHIL COUNTS (PER C.MM.) IN THE 2½-3½ LB. WEIGHT GROUP

No.	lb.	oz.	1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day	14th Day	21st Day	28th Day	35th Day
1	3	7½	0	44	110	198	132	88	22	528	968	1,122	1,144
2	3	1	0	44	99	132	154	154	220	330	396	682	968
3	3	6	0	0	44	22	66	88	110	594	1,056	1,144	
4	2	10	0	22	22	44	66	132	154	550	704	1,012	1,034
5	3	8	0	0	66	110	176	176	154	440	814	1,144	
6	2	11½	0	0	22	22	0	66	110	440	792	1,056	1,320
7	2	15	0	22	44	0	44	88	110	374	682	1,122	1,232
8	3	4½	0	55	11	22	44	66	154	528	902	1,122	1,276
9	2	3	0	0	66	44	66	88	110	396	616	990	1,078
10	3	4	0	22	22	44	66	143	176	440	880	1,056*	1,408

groups of the premature infants and for 20 full term babies. These are not selected cases but are the first members of their respective groups.

Of the full term infants, four (nos. 2, 8, 9 and 10 in Table 4), indicated by asterisks, had counts which showed a significant variation from their previous stable level. Brief histories of these four infants are as follows:

No. 2.—This was a healthy baby boy of a German mother who wished to wean the baby early. She had been given advice at the infant welfare clinic but misunderstood this and gave two large feeds of oatmeal porridge. During the evening of the same day the infant had a widespread macular rash. The blood count on the next day, when the rash was still present, showed 1,247 eosinophils per c.mm. Thickened feeds had been discontinued and the rash disappeared within three days, but the count remained high for four days before falling to normal.

No. 8.—This baby developed chickenpox and the count of 641 per c.mm. was taken three days after the first crop of vesicles appeared. The eosinophil count remained higher than normal until the skin was clear.

No. 9.—A baby boy had had small vomits after feeds since his seventeenth day. There had been one projectile vomit and the weight was stationary. He was admitted to the Royal Aberdeen Hospital for Sick Children with a diagnosis of pyloric stenosis. The count of 27 per c.mm. was found the day after operation and showed satisfactory adrenal function. The infant made an uninterrupted recovery and the eosinophils returned to normal after five days.

Summary
Ninety-three full term babies had daily eosinophil counts performed during the first week of life before discharge from hospital with the mother.

Twenty-five of these babies had counts thereafter at weekly or twice-weekly intervals in their own homes. All blood samples were taken before feeds.

Comparison is made between the counts for these full term babies and for the 75 premature babies previously considered. Most full term babies are born with some circulating eosinophils in contrast

TABLE 2
ABSOLUTE EOSINOPHIL COUNTS (PER C.MM.) IN THE 3½-4½ LB. WEIGHT GROUP

No.	lb.	oz.	1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day	14th Day	21st Day	28th Day
1	3	10¾	0	22	44	44	22	66	88	264	594	902
2	4	4½	0	88	154	308	418	398	418	638	1,078	1,408
3	3	9¾	0	44	44	22	22	66	88	352	264	1,056
4	3	13	0	0	22	22	88	242	352	792	924	
5	3	8½	0	66	88	44	110	110	154	418	1,100	1,100
6	3	15½	22	88	88	44	132	132	198	440	1,122	
7	3	8½	0	0	66	110	176	176	154	462	814	
8	3	11	0	0	0	22	66	110	220	704	968	1,012
9	3	9½	0	44	22	44	132	154	242	572	704	979
10	4	1	0	0	22	22	22	0	44	374	583	506

TABLE 3
ABSOLUTE EOSINOPHIL COUNTS (PER C.MM.) IN THE 4½-5½ LB. WEIGHT GROUP

No.	lb.	oz.	1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day	14th Day
1	4	14⅜	22	44	22	22	88	132	154	572
2	4	10	0	44	88	110	176	176	242	506
3	5	1	110	154	132	198	286	264	374	
4	5	3½	44	66	110	198	154	198	220	374
5	4	9	44	22	0	0	44	88	110	462
6	5	2	66	88	132	308	484	396	418	
7	4	13½	0	0	22	0	44	22	110	528
8	4	8½	88	110	154	154	88	198	286	770
9	5	1	0	44	0	110	154	176	308	484
10	5	2	0	110	88	176	198	242	286	

TABLE 4
ABSOLUTE EOSINOPHIL COUNTS (PER C.MM.) IN FULL TERM INFANTS

No.	lb.	oz.	1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day	14th Day (2)	21st Day (3)	28th Day (4)	35th Day (5)	42nd Day (6)	49th Day (7)	56th Day (8)	63rd Day (9)	70th Day (10)	77th Day (11)	84th Day (12)
1	7	15	24	108	341	282	290	320	308	260	232	165	154	145	149	132	150	142	165	143
2	8	12	0	66	80	180	274	220	198	220	258	251	363	269	1,247*	308	382	420	429	382
3	6	8	65	78	121	90	165	198	198	231	495	242	308	363	336	363	320	308	296	318
4	5	10	0	0	96	250	478	407	440	440	400	440	391	380	401	381	362	394	380	407
5	5	11	22	22	154	198	330	472	616	584	640	726	660	792	626	660	286	721	700	684
6	6	13	66	90	110	132	132	178	198	286	296	361	330	550	425	369	319	352	341	330
7	6	4	×	×	121	132	184	203	396	429	418	396	465	422	399	418	382	431	374	396
8	7	12	99	100	158	220	258	275	240	216	220	198	180	242	341	275	641*	363	264	296
9	6	5	44	70	88	220	350	368	374	297	242	268	27*	264	248	256	265	242	264	270
10	6	12	132	264	352	408	649	689	704	380	286*	596	720	682	720	708	694	710	741	700

× = No count.

to the premature babies who have no circulating eosinophils at birth.

All infants making satisfactory progress show a gradual rise of eosinophils until a high stable level is reached. In the case of premature babies this level is very high, but the full term child has a lower stable level although even this is higher than the figure for adults.

REFERENCE
Burrell, J. M. (1952). *Archives of Disease in Childhood*, 27, 337.

MUSCLE FIBRES IN CHILDREN'S STOOLS

BY

JOHN L. EMERY

From the Department of Pathology, The Children's Hospital, Sheffield

The examination of stools for the presence of undigested fragments of muscle seems to be a reasonable approach to studies of defective digestion. Procedures such as Schmidt's breakfast were at one time familiar clinical practice, but now such methods are rarely considered. This is not surprising, as the literature contains generalizations and indefinite statements; for example, 'The undue presence of meat fibres after a test meal indicated a fault in small intestine activity' (Gradwohl, 1948). Behrendt (1949) summarizes the situation thus:

> 'It is not yet certain whether the presence of a considerable number of undigested muscle fibres in the stools of children with chronic nutritional disturbances is indicative of diminished pancreatic function. Food may move so rapidly to the small intestine in many of these patients that the presence of muscle fibres may be the result of mechanical factors rather than digestive enzymic failure.'

Payne (1952) considers that muscle fibres in children's stools are only of significance if found in large numbers, whereas Lagercrantz (1949) in discussing stools in ulcerative colitis considers the presence of muscle fibres to be signs of poor digestion. Harrison (1947) when discussing tests of pancreatic function considers the examination of stools for muscle fibres as 'simple and valuable'.

In the course of a general survey of children's stools carried out in Sheffield all stools were examined for the presence of muscle fibres. An attempt is made here to determine the incidence of muscle fibres in stools and their relationship to other conditions in these children.

Material and Methods

The material used for this study consisted of just over 1,000 specimens of stools from children of varying ages. The material was identical with that already presented in a study of the normal range of tryptic activity in stools (Emery, 1952). As wide a range of children as possible was obtained, the aim being to secure specimens from a type of child in which a request for the examination of stool would be unlikely. No examinations requested by clinicians were incorporated.

The children received a normal diet, the source of meat in most instances being mincemeat with gravy for lunch. Meat was not given in large amounts.

Three slide preparations were made from each specimen. A small fragment of stool was broken down with saline and then set up with (1) Sudan IV, (2) saturated copper nitrate (Harrison, 1947) and (3) Lugol's iodine. The density of the preparations was gauged so that as far as possible the suspension seen through the microscope filled the field uniformly and without superimposition of faecal masses.

The fibres were only recognized if they showed striations as well as the longitudinal form of muscle fibres. The stool was considered positive (+) if muscle fibres were found in at least two of the three preparations. Muscle fibres were considered to be present in large numbers (+ +) when a large number of muscle fibres were present in all preparations, there being many muscle fibres in every high power field examined, and fibres with ragged ends, the picture conforming to what Harrison describes as true 'creatorrhea'.

An attempt was made to give children fragments of uncooked meat in small muslin bags and later to collect the bags from the stools and examine the contents. This was abandoned because of the disturbance when swallowing the bags—even when hidden in sandwiches or jam.

Results

Muscle Fibres Related to Age. Naturally no muscle fibres were found in unweaned children's stools. In weaned children between the ages of 6 months and 1 year, 97 specimens were examined of which two only contained many muscle fibres and in 66 (69%) none were found. In this age group, 13 months to 2 years inclusive, of 208 examinations, 68 (33%) were negative, 117 (56%) were positive and 23 (11%) contained fibres in large numbers. In the next two years, 44 (27%) of 163 had no fibres, while in children of 5 years and older 118 (24·5%) of 481 examined were negative and 30 (6·5%) were strongly positive. The incidence of muscle fibres does not appear to be significantly affected by age.

Muscle fibres were present in between 67% and 75% of all stools passed in all age groups over a year and in very large numbers in 10% in younger children and 6% in older children.

Muscle Fibres Related to Weight, Height and Nutrition. Seven hundred and eighty-nine specimens were examined from children considered to be of normal weight and 142 from children considered to be under weight. In the normal children muscle fibres were present in 517 (70%) of specimens and in large numbers in 50 (7%), whereas in the underweight children fibres were found in 76 (54%) and in large numbers in four (3%).

Thirty-eight specimens came from children described as being of abnormally small stature and the incidence of fibres in stools (13 negative, 24 +, 1 ++) showed no significant changes from the children of normal height.

Clinically wasted children accounted for 165 stools, and of these 83 (50%) showed no fibres and seven (4%) showed fibres in large numbers. This compared with 797 stools from children of normal nutrition in which 249 (31%) showed no fibres and 48 (6%) fibres in large numbers.

Oedematous patients accounted for 38 stools in which no abnormal incidence of muscle fibres was found.

There appears to be no significant difference in the incidence of muscle fibres in children of differing weights, heights, or general nutritional state.

Disease Groups Related to Presence of Muscle Fibres. Patients were divided into clinical groups (Table 1) depending on the system in which major symptoms presented. In the intestinal groups cases of fibrocystic disease of the pancreas were excluded and the group consisted chiefly of surgical patients.

TABLE 1
DISEASE GROUPS RELATED TO THE PRESENCE OF MUSCLE FIBRES

Disease Group	Muscle Fibres			
	Nil	+	++	Total
Intestinal	45(47%)	46(47%)	6(6%)	97
Respiratory	82(36%)	135(60%)	11(4·8%)	228
Cardiovascular ..	41(22%)	127(69%)	17(9%)	185
Nephritic	13(26%)	31(63%)	5(10%)	49
Others	162(39%)	236(57%)	19(4·6%)	417
'Healthy'	34(31%)	75(67%)	2(2%)	111

The majority of the cardiovascular patients were children with acute rheumatism or congenital deformity of the heart. The 'healthy' children were either the children of colleagues and friends or children admitted to hospital for minor anatomical deformities such as operation for hernia. It was interesting to see that the incidence of stools free of muscle fibres was higher in the intestinal group

(47%) than in any other groups or in the apparently healthy children (31%). However, there appears to be no difference of any significance between the groups of children and the incidence of muscle fibres in stools.

Muscle Fibres Related to Intestinal Passage Time. Using colour markers the intestinal passage time was obtained in 177 specimens. Seventeen of 18 stools passed within 10 hours contained muscle fibres, but 29 of 35 stools passed after 20 and before 30 hours similarly contained fibres (Table 2).

TABLE 2
MUSCLE FIBRES IN STOOLS RELATED TO INTESTINAL PASSAGE TIME

Intestinal Passage Time	Muscle Fibres			
	Nil	+	++	Total
10 hours and less	1	17	0	18
11 to 20 hours	9	41	2	52
21 to 30 hours	3	29	3	35
31 hours or more	13	52	7	72

When the incidence of muscle-free stools passed before 20 hours (10 of 70) and those 20 hours and later (16 of 107) was compared no significant differences were found. It appears that the elimination of muscle fibres is not directly related to the length of time the fibres are in the intestinal tract.

Muscle Fibres Related to Tryptic Activity of the Stools. Both tryptic activity and muscle fibres were recorded on 999 specimens. In 341 no muscle fibres were found, and, of these, 17 stools showed no tryptic activity while 240 showed activity at a dilution of 1 in 100 or more.

When groups of specimens containing tryptic activity in a dilution of 1 in 10 or less and those with tryptic activity at a dilution of more than 1 in 100 were compared, it was found that 37% (70 of 191) of the low tryptic activity group showed no muscle fibres while 33% (240 of 727) of the high tryptic activity group gave a similar result. Thus it would seem that the absence of muscle fibres in stools is not directly related to the tryptic activity of the stools. When, however, the incidence of a large number of muscle fibres was similarly compared, it was found that in the group of 191 with low or absent tryptic activity 22 (11·6%) had gross fibres, while of the 727 with high tryptic activity the number was 35 (4·8%). These figures show a significant difference and suggest a greater incidence of gross muscle remnants in stools with a low or absent tryptic activity.

Muscle Fibres Related to Undigested Starch in Stools. The presence of muscle fibres and starch granules was investigated in 1,000 stools. The starch granules were recorded as being either absent,

present intracellularly, or present both extracellularly and intracellularly.

When the stools containing no starch granules and those with extracellular granules were considered together with the stools containing no muscle fibres and those with very large numbers of fibres, there appeared to be a relationship between the incidence of a large number of muscle fibres and the presence of extracellular starch.

Of 295 specimens containing no muscle fibres 213 (72%) showed no starch granules and 82 (28%) extra cellular granules. Of 45 specimens with much muscle remnant 10 (22%) showed no starch and 35 (78%) extracellular starch.

Discussion

The principal difficulty in a survey of the present type is that the estimation of the amount of creatorrhea present is subjective. In this study an attempt was made to include in the + category numbers of muscle fibres that would normally be considered of no clinical importance, and to reserve for the + + category amounts that on criteria indicated by Harrison (1947) would certainly be considered as being of pathological significance.

The children used in this survey excluded children in whom the diagnosis of fibrocystic disease of the pancreas or coeliac disease could be clinically suggested. When, however, stools from known cases of fibrocystic disease are examined muscle fibres are usually seen but in no greater number than those in the + + category described in this survey.

It was found that on microscopy muscle fibres are present in between two-thirds and three-quarters of stools passed by children of all ages. The presence of the muscle fibres was apparently independent of the nutritional state of the child, and of any particular disease group or notable disease. This figure agrees with the general statements made that muscle fibres in small numbers may be considered to be usual constituents of children's stools. When muscle fibres in large numbers were considered alone the incidence fell to between 5% and 10% of stools but still showed no apparent relationship between nutritional state, age, or disease group.

From a purely clinical and diagnostic viewpoint, that of defect in digestion or pancreatic disease, it seems that the laboratory examination of stools for muscle fibres is a pointless procedure.

The observation that the presence of undigested muscle fibres is related both to the presence of extracellular starch granules and to the lower limits of tryptic activity of the stool suggests that the presence of the muscle fibres in large numbers is not completely fortuitous, in that it appears to be related to other changes in the stools.

No comparable figures appear to be available to say whether or not the creatorrhea found in the children in Sheffield is universal or only of recent origin. It is, of course, possible that the normal digestive economy of the child permits the elimination of undigested food but two other possibilities seem more likely. First, there is anatomical evidence (Andersen, 1938; Blackfan and May, 1938; Emery, 1951) to suggest that minimal degrees of pancreatic disease occur in a sub-clinical and probable reversible form, and second, which may be directly related to the previous point, that our knowledge of diet is inadequate and the diet may contain substances interfering with muscle digestion as glutens (Anderson, Fraser, French, Gerrard, Sammons and Smellie, 1952) interfere with starch. Mellanby (1951) recently pointed out the extent of commercial food contamination with substances of unknown physiological effect. It is believed by many that acrodynia is produced by mercury intoxication from teething powders (Warkany and Hubbard, 1948), and it is possible that mercury is not the only substance that may be harmful and is given unwittingly to children.

In this study we have seen an aspect of digestion which we cannot say is physiological or pathological and it would appear to be as well to keep an open mind on this point until further evidence is obtained.

Summary

A survey was made of 1,000 stools from children showing no clinical features suggesting fibrocystic disease of the pancreas.

Muscle fibres were present in the stools of children in between two-thirds and three-quarters of stools passed. Muscle fibres in what would be considered pathological numbers were also present in between 5% and 10% of stools from similar children.

The creatorrhea appeared to be completely unrelated to age, nutritional state, disease groups, or intestinal passage time of food.

A relationship was found between the presence of many muscle fibres in stools and the presence of extracellular starch granules and reduced tryptic activity.

It is not known whether creatorrhea is physiological or pathological in children, but from a clinical viewpoint microscopic examination of the stools for muscle fibres appears to be a useless procedure.

146 ARCHIVES OF DISEASE IN CHILDHOOD

Ash House Hospital School, the Moss Residential Nursery, and many other individuals for their assistance in collecting specimens of stool.

REFERENCES

Anderson, C. M., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. G. and Smellie, J. M. (1952). *Lancet*, 1, 836.
Andersen, D. H. (1938). *Amer. J. Dis. Child.*, 56, 344.
Behrendt, H. (1949). In *Diagnostic Tests for Infants and Children*, p. 21. New York.
Blackfan, K. D. and May, C. D. (1938). *J. Pediat.*, 13, 627.
Emery, J. L. (1951). *Archives of Disease in Childhood*, 26, 570.
—— (1952). Ibid., 27, 257.
Gradwohl, R. B. H. (1948). *Clinical Laboratory Methods and Diagnosis*, 4th ed., vol. I, p. 1118. London.
Harrison, G. A. (1947). *Chemical Methods in Clinical Medicine*, 3rd ed., p. 264. London.
Lagercrantz, R. (1949). *Acta paediat.*, Uppsala, Suppl., 75, 89.
Mellanby, E. (1951). *Brit. med. J.*, 2, 863.
Payne, W. W. (1952). *J. Gt Ormond Street Hospital*, no. 3, p. 23.
Warkany, J. and Hubbard, D. M. (1948). *Lancet*, 1, 829.

RETROPERITONEAL TERATOMA IN INFANCY

BY

DAVID CHARLES

From the Institute of Obstetrics and Gynaecology, Hammersmith Hospital

The first authentic description of a case of retro-peritoneal tumour is ascribed to Morgagni in 1761. Since that time only 82 cases of retroperitoneal teratomata have been published in the literature.

These tumours lying preaxially must be regarded as pathological manifestations of a physiological process (Nicholson, 1929). Although all three germinal layers are present in teratomata, there is no segregation of tissues. The old theory that these tumours resembled a twin foetus enclosed in another twin is no longer valid although teratoma and host lead an asymbiotic existence. As they contain all three embryonic layers in no standard pattern they must be present at an early stage of foetal develop-ment, and further, as they are extraperitoneal and in the region of the primitive mesentery, retroperitoneal teratomata are in a nidal state before the peritoneum is evolved (Willis, 1935). In the case presented, all somatic tissue elements were present but no regional segregation of tissues was observed and at operation the mesenteric relationship of the tumour was clearly defined.

Spemann (1938) elaborated the theory that primary organizers influenced the embryonic tissues and stated that cells escaping their action are derivatives of or related to the invaginating primitive streak, and thus as teratomata arise in a median or paramedian location they may escape organizer influence. This theory furthers the view now gener-ally accepted that teratomata are not incomplete foetuses but derangements of development arising during the pre-somite stage.

Case Report

S.G. (No. 13071), a girl aged 2 years 2 months, was admitted to the Gloucester Royal Hospital on June 27, 1949. She had been born prematurely after about 36 weeks' gestation. The mother had toxaemia of pregnancy and labour was completed by a forceps delivery. The infant had a left-sided facial paresis which cleared up satisfactorily. Birth weight was 5 lb. 12 oz. The mother had had one uneventful pregnancy seven years previously.

The child developed quite normally and at no time was there concern about her progress.

She was very well until three days before admission to hospital, when her appetite was poor and she complained of pains in the region of the umbilicus. There had been no vomiting or urinary disturbance.

The child's father had a past history of phthisis and five years previously the patient's brother had died of tuberculous peritonitis.

On examination she was seen to be a well built child (weight, 30 lb., and height, 28 inches). The face was highly coloured, and the skin was moist but not hot. There was no cyanosis or icterus. The temperature was 100·4°, pulse 120, and respirations 22. There were no abnormalities of the eyes, ears, nose or throat. The cardiovascular system, respiratory and central nervous systems were normal.

A large, firm, ovoid mass situated to the right of the mid-abdominal line, extending approximately from 2 inches above the umbilicus to 3 inches below, was easily palpable. It was not fixed to the anterior abdominal wall, but seemed to be attached to the coils of overlying gut. The mass had a definite upper border and was separate from the liver. It did not move with respiration and was mobile in the oblique axis from the right iliac fossa to the left hypochondrium. It could not be displaced into the right loin and no pain or tenderness was elicited on palpation. On rectal examination, the mass could be felt on the right side. There was no other clinical abnor-mality.

Investigations, The urine contained a trace of albumin, but no cells or casts were seen.

Blood was Group A Rh positive, and a full count gave haemoglobin 85% (Haldane), red blood cells 4,750,000 per c.mm., leucocytes 12,400 (polymorphs 39%, lympho-cytes 52%, monocytes 4%, eosinophils 4%, basophils 1%). The Wassermann reaction was negative.

A Mantoux test (1/10,000) was negative.

Radiographs of the chest showed no abnormality. Radiographs of the abdomen showed that the right psoas shadow was obscured. The ascending colon, which was outlined by gas, was displaced upwards. On the medial side of the ascending colon a tooth and a small calcified area were seen.

An intravenous pyelogram showed no abnormality.

Operation. Premedication was with 'nembutal', grain 1, and atropine, grain $\frac{1}{100}$. The anaesthetic was nitrous oxide, oxygen and ether.

The abdomen was explored through a right paramedian incision. There was no ascites and the kidneys, liver, gall bladder, spleen and pelvic organs showed no abnormality. An oval tumour lay retroperitoneally in the root of the

147

mesentery of the small gut. The surface of the mass was lobulated but no cystic areas were noted.

The post-parietal peritoneum was incised lateral to the ascending colon and the colon reflected medially. The tumour was then mobilized and removed. The gut showed no evidence of any impairment to its blood supply on completing the operation and the abdominal wound was closed in layers.

At the end of the operation the child's condition showed no cause for concern and convalescence was uneventful. She was discharged from hospital on the twenty-second post-operative day. The child has since been seen at frequent intervals. Clinically and radiologically there is no evidence of recurrence and she is in good health.

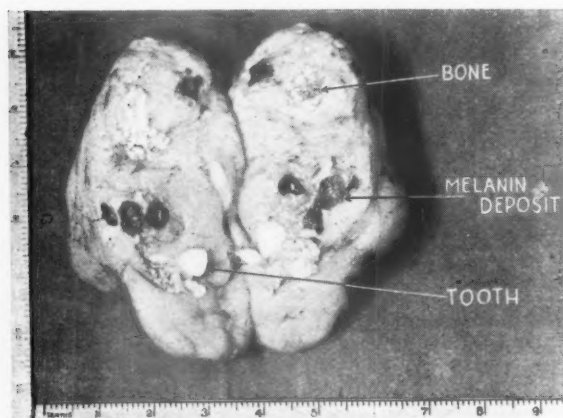**Pathology.** The specimen was a cystic tumour weighing

FIG. 1.—Cross section of teratoma illustrating melanotic deposits and teeth.

17 ounces. It was ovoid, measuring about 5 in. in its long axis. The surface was irregular on the ventral aspect but smooth on the dorsal surface. The tumour was partially covered by fibrous adhesions. On section, the teratoid nature of the tumour was readily observed. Dental, osseous, myxomatous and epidermal tissues were noted.

Tissues derived from all three embryonic layers—ectoderm, mesoderm and endoderm—could be seen microscopically in different parts of the tumour. There was much brown pigmentation (probably melanin) in some areas.

Discussion

In this case, on account of a family history of tuberculous infection the differential diagnosis had to include encysted plastic peritonitis. As the child had a raised temperature this possibility had to be seriously considered. The Mantoux reaction, which was negative using 1/10,000 old tuberculin, did not rule out tuberculous infection but the physical findings together with the Mantoux test made that diagnosis improbable.

A diagnosis of a Wilms tumour was also entertained, but as the mass could not be displaced into the right loin and intravenous pyelography showed no abnormality of the renal tract, this was not considered further.

Arnheim (1943) states that a normal pyelogram does not rule out embryoma of the kidney from the differential diagnosis of an abdominal tumour, but in the literature on Wilms's tumours radiological findings usually settle the diagnosis.

In the present case pressure symptoms due to the tumour were completely absent. The symptoms described in other cases include backache, oedema of the legs and distended veins on the abdominal wall. Again referring to the low grade fever on admission to hospital, which was of unknown origin, Mecray and Frazier (1937) state that it occurs with retroperitoneal tumours but usually indicates the presence of a sarcoma or sarcomatous change. Neither sarcomatous change nor other condition was present in this case so the teratoma must have caused the raised temperature.

The possibility of the mass being a neuroblastoma was considered, but in this condition there is often a history of loss of weight associated with fatigue. Neuroblastomata are usually medially situated and more fixed and nodular in character than teratomata. The radiological finding of a tooth is the main method of differentiating these tumours before operation in the early stages; naturally in the later stages of neuroblastomata secondary involvement of other organs will help in reaching a diagnosis.

Mesenteric cysts also enter into the differential diagnosis and here again radiology is of great assistance as only the large cysts are fluctuant on clinical examination.

Retroperitoneal teratomata are not malignant, but one of their component structures may undergo malignant change at a later date if operative removal at an early stage is not carried out.

Summary

A case of a retroperitoneal teratoma in a child is described.

REFERENCES

Arnheim, E. E. (1943). *J. Mt. Sinai Hosp:*, **10**, 355.
Mecray, P. M. and Frazier, W. D. (1937). *Arch. Surg.*, *Chicago*, **35**, 358.
Nicholson, G. W. de P. (1929). *J. Path. Bact.*, **32**, 365.
Spemann, H. (1938). *Embryonic Development and Induction.* New-haven, Connect.
Willis, R. A. (1935). *J. Path. Bact.*, **40**, 1.

ENCEPHALOPATHY FOLLOWING DIPHTHERIA-PERTUSSIS INOCULATION

BY

JOHN M. SUTHERLAND

From Raigmore Hospital and The Royal Northern Infirmary, Inverness

(RECEIVED FOR PUBLICATION JANUARY 19, 1953)

Involvement of the nervous system during the course of pertussis was originally described by Trousseau in 1877. It is now appreciated that the injection of pertussis antigen may be attended by a similar effect, and the occurrence of encephalopathy has been reported by various authors including Brody and Sorley (1947), Byers and Moll (1948), Toomey (1949), Anderson and Morris (1950) and Grace (1950).

The fact that the administration of any biological drug entails a certain risk has been glossed over in many textbooks, and the low incidence of complications compared with the number of inoculations performed annually has perhaps diminished appreciation of the hazard.

A case of encephalopathy following inoculation with a mixed diphtheria-pertussis vaccine is now reported.

Case Report

The patient, a girl, aged 11 months, was admitted to hospital on May 3, 1952. Ten days before she had received the last of three immunizing doses of suspended diphtheria-pertussis prophylactic (Glaxo). One millelitre of this vaccine, which contains 20,000 million *H. pertussis*, was given at monthly intervals by deep subcutaneous injection, and had previously been free from untoward effect. Vaccination at the time of the first inoculation had resulted in a typical primary vaccinia.

Three days after the last inoculation the child fell from her pram. Although no serious injury was sustained, she became sick and fretful two days later. During the ensuing few days she became increasingly irritable and listless, and ceased to crawl or stand. The child was apyrexial but it was observed by her doctor that active leg movements were lacking and arm movements were weak. No relevant previous history was obtained; there was no family history of epilepsy or of other cerebral disorder.

Clinical examination disclosed that all limbs were weak and flaccid. The child was unable to sit up, stand, or crawl. The optic fundi presented a normal appearance and there was no evidence of disturbed cranial nerve function. The arm reflexes were feebly present; the knee jerks and ankle jerks were equal but over-active. The

plantar responses were flexor. Otherwise, physical examination disclosed no abnormal features.

When lumbar puncture was performed on May 30 a clear fluid under normal pressure was obtained. There was no evidence of spinal block. Cytology was normal, and the fluid was sterile on culture. Biochemical examination furnished the following results: Glucose, 58 mg./100 ml.; chlorides, 673 mg./100 ml.; protein, 38 mg./100 ml. Pandy's test was weakly positive.

On June 2 there was evidence of bilateral pyramidal tract dysfunction. The plantar responses were extensor, the abdominal reflexes could not be elicited, and the tendon reflexes were grossly over-active, particularly on the right side. Right-sided ankle clonus was elicited.

By June 9 there was some evidence of recovery. Improvement continued, and by July 10 evidence of organic nervous disorder was minimal. A further lumbar puncture on that date yielded a cerebrospinal fluid normal in all respects. On this occasion the protein content was 21 mg./100 ml. and Pandy's test was negative.

Clinical examination on November 18 revealed no evidence of neurological disorder. The child was otherwise well and developing normally.

The history of recent inoculations with anti-diphtheria-pertussis vaccine, the flaccidity and the evidence of pyramidal tract dysfunction, suggested the diagnosis of encephalopathy following prophylactic pertussis inoculation.

Although such complications are by no means confined to pertussis prophylaxis, it is doubtful if generalized reactions of this nature occur after injections of the currently available diphtheria prophylactic vaccine alone.

The history of the fall from her pram suggested initially that this infant might have had a traumatic intracranial lesion such as sub-dural haematoma. Although generally encountered in the first six months of life, this condition may occur later in infancy from injuries to the head resulting from falls when the child attempts to stand or walk (Logue, 1951). In the present case, it is possible that trauma played a subsidiary role.

The possible significance of vaccination performed at the time of the first inoculation also merited

consideration. Post-vaccinial encephalomyelitis is generally encountered between the eleventh and fourteenth day after vaccination (Conybeare, 1951). Thus, the long latent period in the present case rendered this diagnosis unlikely. It was considered, however, that vaccination might have exerted a predisposing influence.

Discussion

The pathogenesis of encephalopathy following anti-pertussis inoculation is uncertain. A constitutional tendency or an individual susceptibility is sometimes postulated. This view is not at variance with the widely held belief that an allergic or pathergic state of the nervous system is responsible. Such a state may be an expression of previous specific or non-specific sensitization. It is also conceivable that injection of an antigen might activate a previously latent neurotropic virus. In the case reported the progressive development and the rapid improvement are compatible with an allergic background.

The clinical manifestations vary greatly. Convulsions with or without fever may occur. Muscular weakness, hypotonia, increased tendon reflexes and extensor plantar responses suggest severe cortical dysfunction. In some instances death may result; in others, recovery is attended by evidence of irreversible pyramidal damage, or the later development of epileptic seizures. Some patients recover completely.

Treatment is symptomatic and hence emphasis must be placed on prophylaxis. In the light of our present knowledge the following precautions are suggested: (1) A family or personal history of any neurological disease such as epilepsy should contraindicate anti-pertussis inoculation. (2) Inoculation should be postponed in a child who is suffering from any acute illness, who is in the convalescent state of any of the specific infections of childhood, or who has recently been exposed to such an infection. (3) If any untoward symptoms, and particularly convulsions, follow an injection, subsequent inoculations of pertussis antigen are best avoided. (4) Until more is known of the aetiology and pathogenesis of the encephalopathies it is probably advisable not to vaccinate a child during the period of pertussis inoculations. (5) The dosage should not exceed that recommended by the manufacturers.

In conclusion I would emphasize that it is essential to preserve a sense of proportion since, as pointed out by Cockburn (1951), such complications are very rare and are twice as common in children suffering from pertussis itself. The benefits derived from inoculation outweigh the risks involved, but these risks may be minimized by careful assessment of the history and clinical condition of the child with special reference to the points mentioned above.

Summary

A case of encephalopathy following inoculation with a mixed diphtheria-pertussis vaccine is reported.

The pathogenesis and symptomatology are briefly discussed.

Certain precautions in the use of pertussis vaccine are suggested.

REFERENCES

Anderson, I. M. and Morris, D. (1950). Lancet, 1, 537.
Brody, M. and Sorley, R. G. (1947). N.Y. St. J. Med., 47, 1016.
Byers, R. K. and Moll, F. C. (1948). Pediatrics, 1, 437.
Cockburn, W. C. (1951). Practitioner, 167, 232.
Conybeare, E. T. (1951). Ibid., 167, 215.
Grace, H. B. (1950). Canad. med. Ass. J., 63, 129.
Logue, V. (1951). In Modern Trends in Neurology, ed. Feiling, A., p. 384. London.
Toomey, J. A. (1949). J. Amer. med. Ass., 139, 448.

A HISTORY OF INFANT FEEDING

BY

IAN G. WICKES

PART I. PRIMITIVE PEOPLES: ANCIENT WORKS: RENAISSANCE WRITERS

'All that has been written on the choice of nurses, and the nourishment of children, is hardly anything more than a collection of prejudices.'

N. BROUZET (1755)

Infant Feeding Amongst Primitive Peoples

Anthropological studies show that there is a remarkable tendency to obscure the natural method of infant feeding. This is more readily understandable when it is realized that contemporary primitive tribes are in fact highly civilized, though their form of civilization has evolved along different lines from our own. The known facts have been compiled by Ploss and the Bartels (1935) in their historical and anthropological compendium entitled 'Woman'. The more important points will be reproduced here.

Most savage peoples let several days pass before the mother begins to suckle the newborn baby, and the time interval varies from tribe to tribe, but the average period is four days, and the maximum seldom exceeds nine days. The same kind of taboo on the colostrum is apparent in the writings of both English and French authors of the seventeenth century and it had been handed down to them from Greek and Roman times. The one exception appears to be the Maori tribe who attends to the breasts during pregnancy and begin suckling after delivery (Waller, 1937). Most other tribal women give food to the infant during the interim period and our own practice of giving sugar and water to the newborn is a survival of this custom. In Samoa the whole procedure is highly organized, with an official milk tester, usually an elderly woman, who puts the sample of milk in a dish, adds a little water and two hot stones. If curdling occurs the milk is pronounced poisonous and suckling is further delayed but a suitable bribe usually results in the test proving satisfactory!

The duration of the period of lactation varies considerably from one tribe to another but the average would appear to be from three to four years, though additional foods such as chewed bananas, coconut milk, bread and intoxicating liquors are often started from the earliest age. Hottentots seldom feed longer than about four months, Samoans less than one year, Armenians for one to two years, Australian aborigines for two to three years, Greenlanders for three to four years, Hawaiians five years and Eskimos for about seven years reaching a maximum in King William Land of up to 15 years. In these circumstances a mother may be suckling two or more children of different ages at the same time.

Prolonged lactation would seem to be encouraged by maternal love, the pleasurable sensation experienced, economy, and belief in its contraceptive property. There would appear to be no moral content for, in breast feeding, the wife of primitive man has no feeling of merit or duty; she simply does what she cannot help doing. On the other hand prolonged lactation would appear to be actually abhorrent to civilized man; a note in the *Lancet* (1842) records a case of a woman who suckled a child for three and a quarter years and then developed epilepsy. The attendant physician wrote: 'The worst symptoms of debility at last attended this monstrous proceeding'. The Tyrolese, about 1900, went even further, for at that time breast feeding amongst them was not only not customary but was actually regarded as immoral.

Most primitive women nurse the baby in the horizontal position on their lap, and some use the fingers of their free hand to control the flow of milk. However, the Armenians and several Asiatic races lean over the supine baby, often resting on a bar which runs above the cradle for support. It has been suggested that in this position less air is swallowed, and certainly it is not customary for these women to lift the baby out of the cradle to eructate after a feed. The Hottentots and Fijians carry the child in a cloth on their backs, and having by nature long, pendulous breasts, they are able to toss one over their shoulder to the baby whenever he indicates by crying that he is hungry. In the accompanying illustration the

151

mother is at the same time nonchalantly smoking a pipe. In Japan suckling often occurs lying down, but older children take the breast by standing or kneeling up to the squatting mother.

Fig. 1.—An Armenian suckling her child. Reproduced from 'Woman' Vol. III by Ploss and Bartels by kind permission of Messrs. Wm. Heinemann Ltd.

Wet nurses seem to have been in use from the earliest historical times and women of high rank in most communities have employed them but nevertheless some tribes consider foreign milk to be harmful for the infant, and if the mother dies the Eskimaux plunge the child into the cold sea rather than expose him to this danger. In contrast, some Arab communities pass each infant suckling round to all the lactating women.

In tribes associated with western civilization, such as in Java, the grandmother is expected to put the child to the breast whilst the mother goes out to work but there is considerable doubt as to whether persistent sucking ever stimulates true lactation in this way, though there are several reputed instances which suggest that it sometimes may and there are even reports of fathers successfully suckling.

In Africa and the Cameroons it is customary for the women also to suckle, if need be, domestic puppies and piglets, and the converse, of infants being suckled by animals, has been recognized since the time of Romulus and Remus, and was still practised in France in the last century where babies at L'Hôpital des Enfants Assistés in Paris were regularly put to the teat of asses which were permanently housed in stalls adjoining the ward.

Hoffman wrote at the beginning of the eighteenth century:

'The fiercest animals are rendered mild by human milk, and conversely humans being brought up on the milk of a wild beast become wild and fierce, witness the example of Romulus and Remus.'

The ferocity of Caligula was attributed to the fact that a drop of blood was regularly put on the nipple before he sucked and the bibulous Nero was partly forgiven because he had been reared by a drunken nurse.

The above facts about the breast feeding habits of various tribes are intentionally recorded without embellishment, for speculation upon the remote effects of the feeding mode upon the future life, health and temperament of the growing individual, and hence eventually upon the society and culture of which he forms an integral part, is potentially limitless and therefore liable to be misleading. Nevertheless suggestive facts are constantly being accumulated by workers in the field who converge

Fig. 2.—A Hottentot throws her breast over her shoulder to suckle her child. Reproduced from 'Woman' Vol. III by Ploss and Bartels by kind permission of Messrs. Wm. Heinemann Ltd.

upon the problem from different angles—by anthropologists, paediatricians, psychoanalysts and social workers—and thereby more confidence is being engendered in those who seek to assess the true depth and significance of the problem. Psychoanalysts are continually unearthing incidents which suggest that many important stimuli acting on the very youngest of infants are capable of making permanent and indelible imprints on the psychic pattern which become more and more deeply buried as the years go by and yet are capable in favourable circumstances of sending up bubbles, as it were, which cause ripples of disturbance on the surface. It is reasonable to expect that the emotionally charged atmosphere which is certain to envelop such a vital function as the feeding of a helpless human infant would be a stimulus of the most profound significance capable of moulding the developing character and, to a greater or less extent, of influencing the whole life history of the individual concerned.

Margaret Mead, in her recent study (1949) of the sexes entitled 'Male and Female' (pp. 68-72) approaches the problem as an anthropologist who has lived intimately amongst seven separate South Sea island communities, and she has attempted to correlate feeding habits with community traits. Thus the cannibal Mundugumor actively dislike rearing children, and the mothers push them away from the breast as soon as they are in the least bit satisfied. Their community spends its time quarrelling and head-hunting, and love-making is conducted like the first round of a prize-fight. On the other hand the Iatmul infant (also a head-hunting tribe) is allowed to cry vigorously for a feed, but when at last the breast is given there is no stinting and in this way the mouth becomes an assertive demanding organ. In contrast, the Balinese stuff little piles of pre-chewed banana into the infant's mouth whenever it opens, and this assault is followed in later life by a tendency to cover the mouth and eating is accompanied with great shame. The Arapech, a more docile and contented tribe in New Guinea, suckle their infants whenever they cry and they are never left far distant from some woman who can give them the breast if necessary.

In our own community there is less uniformity of approach to the problem and hence generalizations are less valid, but there is great scope for a team of social anthropologists to observe a series of infants from birth with a view to correlating feeding methods and problems with the later development of personality types and psychoneurotic reactions. Until such research is carried out we can only guess how pervasive an influence infant care can have upon any social structure. It has recently been suggested that Russia's expansionist behaviour depends upon their custom of tightly swaddling the newborn and in this respect it may be significant that our own Empire building was carried out at a time when the same practice prevailed in England.

In the pages which follow we shall record in greater detail the modifications of infant feeding which have developed amongst western peoples, the difficulties which have arisen therefrom, and we shall see the persistence of primitive taboos with the submergence of the natural laws; later we shall observe the impact of science gradually taking effect. The interplay between the primitive and the civilized sometimes produces grotesque results as typified by the illustration of a modern Javanese woman carry-

FIG. 3.—Woman from central Java carrying a suckling of 4 years of age. Reproduced from 'Woman' Vol. III by Ploss and Bartels by kind permission of Messrs. Wm. Heinemann Ltd.

ing a 4-year-old suckling boy who is smoking a cigarette between feeds!

Earliest Writings on Infant Feeding

F. H. Garrison, writing the introductory chapter on the *History of Pediatrics* in Abt's 'Pediatrics' makes a comprehensive study of the references to paediatrics in the earliest medical writings which have been handed down to us from the ancient civilizations.

The Papyrus Ebers (c. 1550 B.C.) is the earliest medical encyclopaedia from Egypt and it includes a very small paediatric section which contains one short prescription concerning breast feeding:

> 'To get a supply of milk in a woman's breast for suckling a child: Warm the bones of a swordfish in oil and rub her back with it. Or: Let the woman sit cross-legged and eat fragrant bread of soused durra, while rubbing the parts with the poppy plant.'

From this brief reference we can deduce that failure of lactation was a definite problem in ancient Egypt which was not entirely solved by the use of wet nurses or the adoption of artificial feeding, a hazardous procedure in those days. Later, in the Ptolemaic period, Greek influence probably resulted in an increased use of slaves as wet nurses whose responsibility it was to breast feed their charge for about six months and then to use cow's milk. In the Cairo museum there is a nursing flask of the Alexandrian period (second century) and perhaps these were used for the rearing of foundlings who, if they survived, were destined to become gladiators or prostitutes.

Indian Brahminical medicine had an excellent and well systematized paediatric section, and in the 'Susruta' (second century B.C.) it is made clear that it was customary to evacuate the meconium by giving honey and clarified butter during the first four days of life whilst the colostrum was expressed and discarded. Normal breast feeding was begun on about the fifth day. If a wet nurse was later required it was recommended that a lactating woman should be selected from the same caste as the infant, with well shaped breasts and with all her own children living. An infant should not be put to the breast of a woman who was feverish, dyspeptic, hungry or pregnant, and the milk should be tested and found to be easily miscible with water, thin, cold, clear, without froth or shreds and the colour of a conch shell.

In Israel children were regarded as a blessing and breast feeding as a religious obligation. It seems probable that the average duration for suckling was about three years (2 Maccabees 7, 27) and the hire of wet nurses was clearly well organized one

thousand years before Christ (Exodus 2, 7). The common belief in purging the newborn is preserved in Isaiah (Isaiah 7, 14) but there is no mention of artificial feeding anywhere in the Talmud.

In Homeric Greece (950 B.C.) wet nurses were in frequent demand, particularly by women of the higher classes, in whose households they came to hold a position of great responsibility with authority over the slaves and often with prolonged care of their charges up to adolescence. The writings of Hippocrates (460-370 B.C.) and his school contained little about infant feeding apart from some of the 32 aphorisms which, according to W. H. S. Jones, have been put together by scribes from later writers under the general heading 'On Dentition'. The first five are worth reproducing here:

> I   Of children, those that be well nourished by nature, suck not milk in proportion to their fleshiness.
> II   Gross feeders that draw much milk gain not flesh in proportion.
> III   Of sucklings, they that pass much water are least inclined to sickness.
> IV   They that have the belly much moved and good digestion withal are the healthier: they that have scant movement, and being gross feeders are not nourished in proportion are sickly.
> V   In those that vomit much milky material, the belly is confined.

Hippocrates believed that the foetus learned to suck *in utero* and that this accounted for the passage of meconium and the presence of the sucking reflex at birth. He advised that

> 'Children and infants for a long time should be washed in warm water, and for drink should be given wine diluted with water and not quite cold; this should be given because it does not distend the belly and cause wind. These things are to be done to lessen the liability to convulsions . . .'

The next great writer of importance whose works have come down from the Graeco-Roman period is Soranus of Ephesus who lived in the second century A.D. and who produced a treatise on gynaecology and obstetrics which included no fewer than 23 chapters on mothercraft, infant feeding, teething and children's diseases which served as a prototype for the next 1,500 years. Soranus dealt in full with the choice of a wet nurse, the regimen for nurses, salting of the newborn and many other topics. He included the first description of the nail test which he probably did not originate but which has been handed down the centuries under his name from book to book. He recommended withholding the breast during the colostrum period just as the earlier Indian writers did, and at the age of 6 months he advocated the addition of bread crumbs, diluted wine, soups and eggs. There is no complete English

translation of his works, but his influence upon the Renaissance writers will be plainly discernible in the next section. There is a full French translation by Dr. Herrgoth (1895).

Galen (A.D. 130-200) wrote a chapter on infant feeding which, so far as I am aware, has never been translated into English but he is more particularly important for his general influence on medical thought in the Middle Ages. His conception of the fundamental principles of the natural world, or elements (air, fire, earth and water), which were respectively cold, hot, dry and moist dominated all branches of medicine for many centuries. A combination of one quality from each pair produced a complexion, and each had its appropriate humour thus:

Complexion	Qualities	Humour
Sanguine	Hot and moist	Blood
Phlegmatic	Cold and moist	Phlegm
Choleric	Hot and dry	Yellow or green bile
Melancholic	Cold and dry	Black bile

Children were considered to be phlegmatic at first, becoming sanguine and choleric with growth; they had to be treated accordingly.

Oribasius (A.D. 325-403) in his treatise to Eunapius Lib. 5 was one of the first writers to reproduce Soranus almost *in toto*, but Galen's influence is also apparent where he advises against giving meat to infants because it 'creates phlegm'.

The medical writings of Paulus Aegineta (?A.D. 625-690) have been fully translated by Francis Adams; they comprise seven books of which the first is concerned with infant feeding. Most was copied from Oribasius who in turn plagiarized Soranus, but it is worth summarizing here the main points with which he dealt. In choosing a wet nurse he recommended that she should be between the ages of 25 and 35, with well developed breasts and chest, and have been recently delivered of a male child. She should avoid salty and spicy foods, venery and debauchery, and she should take regular exercise employing the arms and shoulders by grinding or working at a loom. In addition to the nail test he advised adding rennet to the milk in a glass, allowing the cheesy sediment to settle, and comparing the serous supernatant fluid with the sediment. They should be roughly equal in quantity, but if the latter exceeds the former the milk will be indigestible, and if vice versa then the milk is too weak. If on the other hand the milk was too thick the mother should be given emetics to evacuate the phlegm, and if it was offensive it should be expressed and the mother fed on fragrant food and wines.

The Arabian school, which flourished about 200 years after Paulus, was represented by Rhazes (850-932), Avicenna (980-1037) and Averroes (1126-1198) who were more interested in children's diseases than in infant feeding but they served to bridge the gap between the Graeco-Roman and Renaissance writers. Rhazes attributed 'Mater Puerorum' to the taking of too much milk and thereby set a precedent for many subsequent writers to cite overfeeding as the cause of numerous disorders. Avicenna advised purging the nurse if the infant ailed.

The practice of preventing the newborn infant from taking colostrum and the giving of sugar instead, which is plainly contrary to nature, has therefore been prevalent since the dawn of civilization and, as we have seen, it is still almost universally adhered to by contemporary primitive tribes. In the writings we have so far referred to, there is very little mention of artificial feeding yet the discovery of feeding vessels from 2000 B.C. onwards suggests strongly that animal milk was in fairly common use. Many clay vessels have been found in the graves of Roman infants and some, from the first to the fifth century A.D., have been accurately dated with the aid of coins found along with them. It is difficult to account for this widespread omission, but perhaps the most likely explanation is that the milk was not modified in any way and hence no instructions for giving it were required. In any case wet nurses were the great standby; their employment by the Roman patricians caused Tacitus to inveigh firmly against their excessive use. Later writers have regarded this practice as a cause or a symptom of the decline that was to follow and have used similar arguments to warn our own civilization of its impending doom.

Aulus Gellius in 'Attic Nights' (translated by J. C. Rolfe), also records how the philosopher Favorinus called at a Roman's house to congratulate him on the birth of a son and he relates the arguments whereby Favorinus attempted to convince the grandmother that her daughter should suckle the child. In a long dissertation he asserted that to refuse the breast was as wicked as to procure an abortion, and he clearly believed in the conveyance of character via the milk which he used as an argument against the employment of a nurse.

The ancients, therefore, sowed the seeds of many of the superstitions and practices which embellish infant feeding even today, but they blossomed most strongly in the Middle Ages.

Renaissance Writers

We can pass straight from the ancients to the Renaissance period for there is no surviving work

from the Middle Ages relevant to our subject nor is it likely that anything of importance was written. The year 1472 marks the beginning of the output of printed works on paediatrics (Still, 'History of Paediatrics' p. 58), but all the earlier ones were in Latin and nearly a 100 years were to pass before the first book in English on the subject appeared.

Paul Bagellardus (?-1492) wrote the first of the paediatric incunabula which was printed in Padua in 1472. It was largely compiled from the ancients and contained the usual references to the nail test and the characteristics of a good wet nurse. Hiccoughs, diarrhoea and vomiting were all attributed to over-
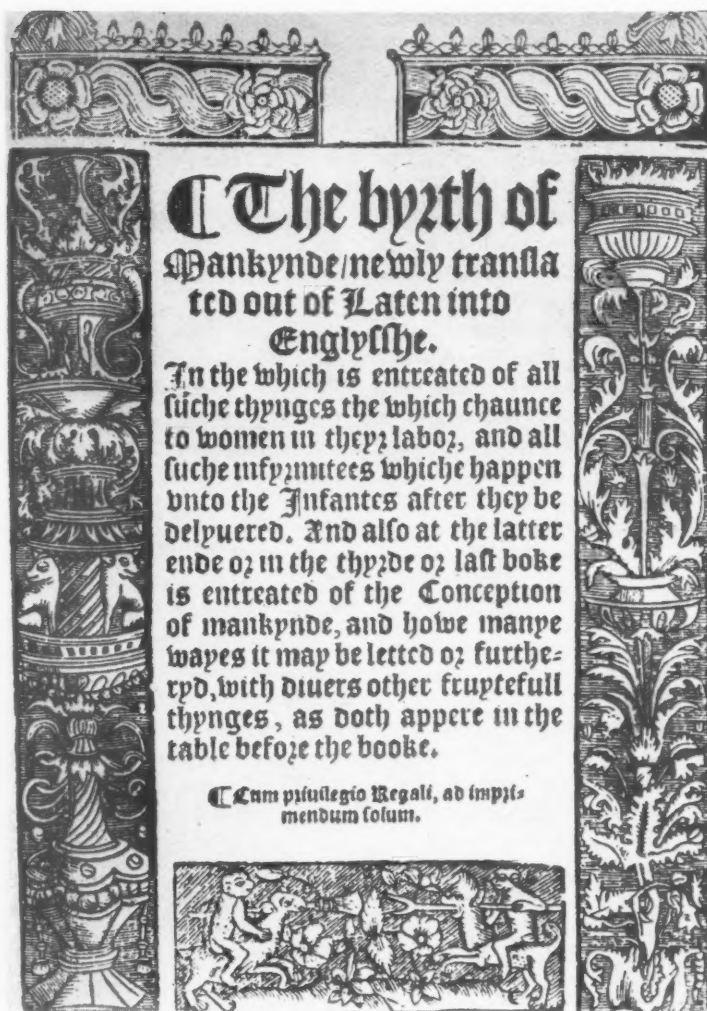

FIG. 4.—Title page of the English translation of Roësslin's 'Rosegarten' by Richard Jonas, 1540. Reproduced from 'History of Paediatrics' by Still with the kind permission of the Oxford University Press.

page is reproduced here and the following quotation comes from the First Boke, Cap; X, folio lix;

'Avicen avyseth to geve the chylde sucke two yeres / howe be it amonge us most commenlye they sucke but one yeare. And when ye wyll wene them / then not to do it sodenly / but a lytell and lytell / and to make for it little pills of bread and sugre to eate and accustom it so / tyll it be able to eate all manner of meate.'

The above passage is of particular interest and value because of the fact that the author definitely states that he is describing contemporary custom. All too frequently the medical historian has to assume that the author is describing contemporary methods whereas in fact he may just

feeding while viscous milk gave rise to constipation which was to be treated with a suppository made from powdered mouse excrement. Ruhräh ('Paediatrics of the Past' pp. 34-70) gives a full quotation from Bagellardus.

E. Roësslin (?-1526), who lived in Worms, wrote the first printed book on obstetrics and, as was the custom with the ancients, it included a section on paediatrics which was mainly a translation into Latin from Metlinger (c. 1450-1492), who had written the first book in German. Roësslin's 'Rosegarten' as it is called was translated into English by Richard Jonas in 1540 with a dedication to Katherine Howard, wife of Henry VIII. It was later reprinted by Thomas Raynalde entitled 'Byrthe of Mankynde'; a photograph of the title

as well be endeavouring to introduce a new scheme which he considers to be an improvement upon the existing state of affairs which is too well known to require further mention. It is for this reason that a history of infant feeding can never hope to be very much more than a chronological account of the relevant bibliography; further extension into the everyday methods of the common people is usually pure speculation. Forsyth, speaking at the Royal Society of Medicine in 1910, fell into this trap when advancing his thesis that not only was the incidence of breast feeding steadily declining, but also that the duration of lactation had been gradually curtailed from about two years in Elizabethan times to about nine months by 1900. The above quotation from the 'Rosegarten' shows clearly how much he was at fault.

Thomas Phayer (1510-1560), generally known as the father of English paediatrics, wrote the first English textbook on the subject entitled the 'Boke of Children'. This was originally bound with his 'Regiment of Life' and was, according to Still, first published in 1546 but Caulfield asserts that there is a copy in the Huntington Library, California, dated 1544. The last edition appeared in 1654 and the book therefore held its popularity for a century. It is freely borrowed from Jonas' translation of Roësslin who in turn had plagiarized Metlinger, who himself had derived his main inspiration from the ancients, relayed largely through the Arabian school. Phayer's description of the nail test and his remedies for increasing breast milk are copied almost word for word from the earlier work. Copies of both works can be seen and compared at the Wellcome Historical Medical Library; it is interesting to note that the 'Rosegarten' is paginated as folios, whereas in the 1546 edition of Phayer (variously spelt Phaer, Faer, Fayre, etc.) the pages are unnumbered. Phayer wrote about eight pages on infant feeding before passing on to the diseases of children and his pleasing style makes a quotation of the major part well worth while.

He begins by avowing his disinclination to deal with the hygiene and feeding of infants at all since in his day these matters were completely dominated by the midwives, but he summons enough courage to proceed notwithstanding. In the introduction he gives expression to the widespread belief of that period that temperament and morals, in addition to diseases, are conveyed by the milk of the nurse:

> 'In the meane season for confinitye of the matter, I entend to write somewhat of ye nourse, and of the milke, with the qualityes, and complexions of ye same, for in that cōsisteth the chief pointe and summe, not only of ye mayntenaunce of health, but also of the fourmyng or infectyng eyther of the wytte, or maners, as the Poet Vergyl when he would describe an uncurteys churlyish and a rude cōdishioned tyraunt, dydde attribute the faute unto the gyver of the mylke . . .
>
> And, as writeth Aulus Celius, Phavorinus the Philosopher affirmeth, if ye lambes be nouryshed with ye milke of goates, they shall have course wolle, like the heare of goates: and yf kiddes in lyke maner sucke upon shepe ye heare of them shalbe soft lyke wolle. Wherby it doth appeare, that the mylke and nouryshyng hath a marveylous effecte in chaunging the complexion . . .'

Phayer then follows this up naturally with the traditional criteria for choosing a wet nurse, the appearance of sound milk, and of course a description of the famous nail test:

> 'Wherfore as it is agreing to nature, so it is also necessary and comly for the oune mother to nourse the oun child. Which if it maye be done, it shall be most comendable and holsome, yf not ye shall be well advised in taking of a nourse, not of yll complexion, and of worse maners: but such as shall be sobre, honeste and chaste, well fourmed, amyable and chearefull, so that she may accustome the infant unto myrthe, no dronkard, vycyous nor sluttysshe, for such corruptethe the nature of the chylde.
>
> But an honest woman (such as had a man chyld last afore) is best not within two monethes after her delyveraunce, nor approchyng nere unto her time againe. These things ought to be cōsidered of every wyse person, that wyll set their children out to nource. Moreover it is good to loke upon the milke, and to se whether it be thicke and grosse, or to much thinne and watrye, blackysshe or blewe, or enclynynge to rednesse or yelowe, for all such are unnaturall and evyll. Likewise when ye taste it in your mouthe, yf it be eyther bytter, salte, or soure, ye may well perceyve it is unholsome.
>
> That milke is good, that is whyte and sweet, and when ye droppe it on your nayle, and do move your finger, neyther fleteth abrod at every stering, nor wyll hange faste upon your naile, when ye turne it downeward, but that whyche is betwene both is beste.
>
> Somtime it chaunceth that the milke wasteth, so that ye nource can not have sufficiente to susteine the child, for the which I wil declare remedies leaving out the causes for brevity of time.'

Since the problem of the causes of failing lactation is still unsolved today it is disappointing that Phayer had no time to recount them, but under the heading 'Remedie appropriate to ye encreasyng of Mylke in the Brestes' he recommends 'parsneppe rootes', 'fenelle rootes sodden in broth of chicken and afterward eaten with a little fresshe butter', 'rice sodden in cow's mylke', 'the powder of earthwormes dryed and dronken in the broth of a neates tonge', and 'the broth of an olde cocke, with myntes, cynamone and maces'. If all these fail, the local application of plasters of fenell may be efficacious.

Sir Thomas Elyot (1490-1546), a diplomatist in the court of Henry VIII and author of the 'Castel of Helth', of which there is a copy at the Royal College of Physicians, also gave expression to the popular belief in the moral danger inherent in employing a wet nurse (quoted by Still, 1931, p. 307);

> 'For as some auncient writers do suppose, often times the childe soukethe the vice of his nouryse with the milke of her pappe.'

Thomas Muffett (1553-1604) in his book 'Healths Improvement' (1584) draws attention to the medicinal use of breast milk:

> 'Neither is women's milk best onely for young and tender infants, but also for men and women of riper years, fallen by age or by sickness into compositions. Best I mean in the way of nourishment, for otherwise asses milk is best.'

He later describes the effect of the nurse's temperament on the ailing Dr. Caius:

'What made Dr. Cajus in his last sickness so peevish and so full of frets at Cambridge, when he suckt one woman (Whom I spare the name) froward of conditions and of bad diet; and contrariwise so quiet and well when he suckt another of a contrary disposition.'

Muffett believed that breast milk was 'converted from the superfluity of the blood', and 'seemeth to be nothing but white blood'. He strongly favoured breast feeding and on page 120, Chapter XIIII of the 1655 edition he warned against the use of animal milk:

'. . . Aegyrthus, who being fed in a Shepheards Cottage only with goat's milk, waxed thereupon so goatish and lecherous, that he defiled not only Agamemnon's bed, but also neighed (in a manner) at every man's wife.'

The rest of the chapter on milk is concerned with a long discussion on the qualities of various types of animal milk, and the usual description of the virtues desirable in a wet nurse, to which he adds, 'Such a nurse is sooner wished of than found'.

On the continent Simon de Vallambert wrote the first French treatise on the subject entitled 'De la Maniere de Nourrir et Gouverner les Enfans des leur Naissance' (1565) in which he recommended feeding cow or goat's milk through a horn after the third month of life, and he was the first author to mention the possibility of the transmission of syphilis between nurse and infant. He attacked the prevalent custom, handed down from Avicenna's day, of the nurse chewing the food before feeding it to the child because he believed that this generated worms. In Italy O. Ferrarius wrote 'De Arte Medica Infantum' in 1577 which contains the first picture of a breast pump consisting of a receptacle with an opening for the nipple, and a long spout reaching up to the mother's mouth, and H. Mercurialis, the misogynist, wrote 'De Mortis Puerorum' in 1583 in which he recorded that lactation may last for two or three years but most women (whom he described as stupid and always making mistakes) gave pap by the third month and stopped breast feeding by the thirteenth in contrast with the old days when, for example, Plotinus at the age of eight used to run from his tutor to his nurse and clamour for the breast.

We have seen enough of the fifteenth and sixteenth century writings to realize that little or nothing was added to that which had been handed down from the Graeco-Roman period, but the advent of printing together with the use of the English, French and German vernaculars ensured a much wider dissemination of the older works than had previously been possible.

Some historians, such as Forsyth, have noted the paucity of details about artificial feeding and have concluded that animal milk was not used for babies during this period. This omission, however, was also noticeable in the classical works and since the Renaissance writers followed the ancients so closely it is hardly surprising that it was perpetuated. We have ample evidence of a concrete nature of the use of animal milk in Roman times, and medieval prints depict the use of a cow's horn as a feeding bottle such as de Vallambert describes. We have no knowledge whatsoever as to the details of artificial feeding, nor do we know what proportion of society was able to employ wet nurses instead, but there can be little doubt that breast milk was by no means the only food commonly given to young infants.

[A full bibliography will be published with the last section of this paper.]

BOOK REVIEWS

Survey of Clinical Paediatrics. By LAWRENCE B. SLOBODY. (Pp. 471. 63s.) London: McGraw-Hill Publishing Co. 1952.

This book, which is attractively produced in an effective combination of serif and sanserif types, is designed as a paediatric handbook for students and practitioners. Although there are already enough full-scale textbooks of paediatrics, there is still a place for an introductory work of this nature. While many of the sections, such as those on fluid and electrolyte balance and on normal growth and development, are models of compression and lucidity, the quality of the work as a whole is uneven, and it contains many statements which will mislead the public to whom it is directed. The following are some of the detailed criticisms which occur to the reviewer.

Although it is stated that breast feeding is 'probably superior to artificial feeding', insufficient emphasis is given to the desirability of breast feeding from all aspects in the first three months of life.

The various syndromes of vitamin deficiency are succinctly described, but their rarity under normal conditions of care is not brought out clearly: and elsewhere, in a discussion of anorexia, a pusillanimous attitude to the effect of the popular press and of advertisements on the nervous parent is shown in a recommendation of vitamin therapy in the presence of this symptom for the purpose of allaying parental fear of vitamin deficiency.

When the routine immunization measures which should be carried out are outlined, the efficiency and safety of pertussis immunization is too lightly assumed.

Obesity is unjustifiably included among the minor psychiatric symptoms of childhood, and is described as being in almost all cases solely due to a pathologically high caloric intake; this well worn hypothesis has never fitted the facts and is misleading. The value of the section on disorders of speech, reading and hearing, appears to have been damaged by over-compression; even within the space allotted it could have been more informative. The chapter on treatment deals almost entirely with antibiotics and cortisone. Useful tables of drug dosage are given, and a quick reference table giving the emergency treatment of 25 types of poisoning is included.

Although the proper care of the newborn baby is well described, an astonishingly naive attitude to natural mother-baby relationships is shown when what is called 'the rooming-in plan' (in which the newborn baby is not kept apart from his mother in the first few days of life) is described as if it were a new and untried technique of no economic and as yet unproven psychological value.

In many places space has been well saved by giving aetiologies in list form. Nevertheless an opportunity has been missed here of imparting valuable information without any expenditure of space, for these lists are not in any significant order, nor do they make any reference to the extent of our present ignorance of aetiology. For example, under the heading 'Congenital Disorders' it is not stated that we are quite ignorant of the aetiology of nine out of ten cases, and the first three causes listed are (1) infection during pregnancy, (2) poor maternal diet, and (3) maternal exposure to radiation. Exactly the same strictures apply to the paragraph on mental deficiency; and peptic ulcer heads the list of causes of melaena.

The sections on prematurity, infection and upper respiratory infection are good, but there is no general account of the special nature of infection in the early weeks and months of life; and it is surprising to see that while the tuberculin patch test is described quite rightly as unreliable, no reference is made to the tuberculin jelly test which carefully performed gives results which correlate very closely with those of the 1/1,000 intra-dermal Mantoux test. The period of isolation of cases of poliomyelitis is admittedly arbitrary, but the minimum of one week here recommended is hardly safe. The statement that nasal drops are injurious to the mucous membrane if given for more than three to four days is not borne out by experience so far as aqueous drops are concerned and seems likely to encourage inadequate treatment of recurrent upper respiratory infections.

In the chapter on gastro-intestinal disease the periodic syndrome is dismissed more briefly than the importance of its differential diagnosis and management warrant in a six-line paragraph under the heading 'Cyclical Vomiting'; and the fluid intake recommended in the treatment of gastro-enteritis ($2\frac{1}{2}$ oz. per lb. body weight per day) is inadequate to allow for rehydration and for continued loss in the stools; nor is any specific reference made to the danger of rapid rehydration with potassium-deficient fluids. A list of seven liver function tests is not accompanied by any estimate of their value in infancy, which is low. The section on intestinal obstruction has been unbalanced by the omission of Hirschsprung's disease and fibrocystic disease of the pancreas as causes.

The chapter on 'allergic diseases' is commendably short, but nevertheless the value of allergic investigations and anti-allergic treatment is somewhat overstressed in relation to that of long term physical and psychological care, especially in the case of asthma.

This book in its present form could not be put unreservedly in the hands of students as a sound introduction to paediatrics, but fairly extensive revision could greatly improve its value.

Garrod, Batten and Thursfield's Diseases of Children 5th edition. Edited by ALAN MONCRIEFF and PHILIP EVANS. (2 vols., pp. 1973: £7 the set.) London: Edward Arnold and Co. 1953.

After the recent appearance of two new textbooks from the Continent, new editions of established works from America, and smaller volumes of child health and disease in this country, it is a pleasure to welcome the fifth edition.

159

of the standard British textbook of diseases of children. For this Dr. Philip Evans joins Professor Moncrieff as editor in place of Dr. Donald Paterson, regrettedly departed to Canada.

The growth of the subject of paediatrics is exemplified in this as well as in the other major textbooks by an increase in size and unfortunately in price. This trend was shown in the 1949 edition and shows no sign of abating. It is timely that the present edition should appear so soon after the other works, and the reader who is making up his mind to spend what is relatively a large sum on a paediatric textbook cannot now complain that his choice is restricted.

In 'G., B. and T.', as 'Diseases of Children' is usually known in this country the intending buyer will find all that is best in British paediatric practice attractively produced and edited to show a minimum of overlap. As is inevitable when there are 50 contributors, there is a certain amount of unevenness, and some sections, in spite of the lapse of only four years between this and the previous edition, are scarcely up to date. As long as textbooks are put on the market in a bound form, so long will much of their matter necessarily be copied from one edition to another, while the rapidly moving sections will be out-dated by the time they appear in print. There is much to be said for the loose-leaf system adopted recently by Debre and Lelong whereby those branches of paediatrics in which the more rapid advances are being made can be brought up to the minute by the re-writing of a small section of the book rather than a completely new edition.

'Diseases of Children' by Moncrieff and Evans contains some new chapters and shows evidence throughout of careful revision of practically all of them, and the book is worthy to hold its place not only by comparison with its previous editions but also with the various foreign works. It is likely to retain its place as the standard British paediatric textbook for many years to come.

The 1952 Year Book of Pediatrics. Edited by SYDNEY S. GELLIS. (Pp. 410 plus index; 112 text figures. 42s.) Chicago: The Year Book Publishers Inc. 1952.

The new editor of this popular Year Book, Dr. Sidney S. Gellis, is to be congratulated not only on maintaining the tradition set by his editorial predecessors, but on the vast amount of knowledge which has been condensed into such a small space.

What are regarded as advances—and here the editor has a most invidious task—are presented under the customary headings which will be familiar to readers of the previous editions. As usual, the abstracts are preponderantly from the American literature, there being some four American articles to every one from the rest of the world. This may be an index of the relative amounts of paper devoted to paediatrics by the different parts of the world, the editor's assessment of the relative value of the world's contributions to paediatric literature, or may simply represent the scope of his reading. As in previous years, many of the articles are followed by observations of selected commentators; and as is also customary, some of these are helpful, many are patronizing and others just naive. The value of the abstracts would not be reduced if these comments were omitted.

Fanconi and Wallgren's Textbook of Paediatrics. Edited by W. R. F. COLLIS. (Pp. 1,104; illustrated. £7 7s.) London: Wm. Heinemann. 1952.

Sixteen contributors from nine different European countries combine to present this textbook on the practice of continental paediatrics. We in this country are used to British and American textbooks and the language difficulty has prevented many of us from being fully acquainted with continental practice. For this reason an English edition of Fanconi and Wallgren's textbook, edited by Dr. Collis with the help of the translator, Dr. Kawerau, will be welcome. The differences in British and Continental practice appear more those of detail than of principle, but paediatricians here will be glad to have available a book of reference by which to compare the two.

It is well-nigh impossible for one person to review the contents of a compendium such as this, particularly when the contributions by such well known workers in their own widely separated fields reach such a high standard. Suffice it to say that paediatricians wanting to know anything about anything will find it here. Misspellings and mispunctuation abound throughout the book, as do uniformly excellent illustrations, and the colour photographs reach a very high standard. Seven guineas is a lot to pay for a book, but in this one gets a lot for one's money.

Office Psychiatry. By L. G. MOENCH. (Pp. 310; illustrated. £2 5s.; U.S.A. $6.00.) Chicago: The Year Book Publishers: Distributed in Great Britain by Interscience Publishers Limited. 1952.

This is not, as its title might suggest, an attack on the lunatic bureaucracy, but a readable account of psychiatry intended for the general practitioner. The intention is excellent for there are not enough psychiatrists to deal with all the neuroses and psychosomatic disorders, and most of these can be treated by doctors who are not specially trained.

Only the first two chapters are devoted to childhood and adolescence, but many mental troubles showing up in adult life have their roots in childhood, and this view recurs throughout the later chapters. Almost any paediatrician could spend an entertaining and useful evening browsing over the book, skipping the banal or turgid passages and enjoying those which stimulate or intrigue. Part of the pleasure would be anthropological; the American adolescent grows up so differently from our own that many of the statements cannot be applied directly to disorders of behaviour seen in the British way of life. The difference may be perceived in the illustrations. At first sight they look as though they might have been taken from an American comic strip or the humorous page of *The Saturday Evening Post*, yet they are true illustrations; they add light to the instruction given in the text, and if their secondary purpose is to catch the eye of the customer in the book shop, there's no great harm in that.